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S. Hrg. 103–747

ASSESSING THE EFFECTS OF ENVIRONMENTAL TOBACCO SMOKE

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THE

SUBCOMMITTEE ON
CLEAN AIR AND NUCLEAR REGULATION
OF THE
COMMITTEE ON
ENVIRONMENT AND PUBLIC WORKS
UNITED STATES SENATE

ONE HUNDRED THIRD CONGRESS
SECOND SESSION

ON

S. 262

A BILL TO REQUIRE THE ADMINISTRATOR OF THE ENVIRONMENTAL PROTECTION AGENCY TO PROMULGATE GUIDELINES FOR INSTITUTING A NONSMOKING POLICY IN BUILDINGS OWNED OR LEASED BY THE FEDERAL GOVERNMENT

AND

S. 1680

A BILL TO AMEND THE TOXIC SUBSTANCES CONTROL ACT TO PROTECT THE PUBLIC FROM HEALTH HAZARDS CAUSED BY EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE, AND FOR OTHER PURPOSES

MAY 11, 1994

Printed for the use of the Committee on Environment and Public Works

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U.S. GOVERNMENT PRINTING OFFICE
80–075cc WASHINGTON : 1994

For sale by the U.S. Government Printing Office
Superintendent of Documents, Congressional Sales Office, Washington, DC 20402
ISBN 0-16-045940-0

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ASSESSING THE EFFECTS OF ENVIRONMENTAL TOBACCO SMOKE

WEDNESDAY, MAY 11, 1994

U.S. SENATE,
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS,
SUBCOMMITTEE ON CLEAN AIR AND NUCLEAR REGULATION,
Washington, DC.

The committee met, pursuant to notice, at 9:39 a.m. in room 216, Hart Senate Office Building, Hon. Joseph I. Lieberman [chairman of the subcommittee] presiding.

Present: Senators Lieberman, Lautenberg, Faircloth, and Chafee.

OPENING STATEMENT OF HON. JOSEPH I. LIEBERMAN, U.S. SENATOR FROM THE STATE OF CONNECTICUT

Senator LIEBERMAN. The hearing will come to order.

I would like to welcome the witnesses and everyone else to this hearing of the Subcommittee on Clean Air and Nuclear Regulation of the Committee on Environment and Public Works.

We are here today to discuss the possible effects on nonsmokers of environmental tobacco smoke, ETS, also known as secondhand smoke. Tobacco smoke directly inhaled is dangerous to the health of those who directly inhale it, to smokers. In this hearing, we are going to turn to a related public health problem, and that is the health effects on those who do not smoke but inhale environmental or secondhand tobacco smoke that is emitted by the burning end of a cigarette, pipe, or cigar, or exhaled from the lungs of smokers into the environment.

We approach this subject as part of this subcommittee's interest in the quality of our indoor air. Americans spend 90 percent of our time indoors. EPA and its Science Advisory Board have consistently ranked indoor air pollution as one of the top four environmental risks to the health of the American people. Secondhand smoke is clearly a significant component of that threat. The Senate has passed a comprehensive indoor air quality bill, and this committee has also reported our legislation that addresses the particular risks of indoor radon.

The committee now has pending before it two bills introduced by Senator Lautenberg of New Jersey to restrict indoor smoking. The first bill, S. 262, would require the EPA Administrator to promulgate guidelines for instituting a non-smoking policy in Federal buildings. The second bill, S. 1680, would require all public facilities to implement policies restricting smoking. That would include some private facilities, such as restaurants.

The purpose of the hearing this morning is to provide the subcommittee with evidence to enable us to make informed judgments on these two bills that have been introduced by Senator Lautenberg.

According to the EPA, secondhand smoke consists of not only nicotine and tar, but also about 4,000 other substances, approximately 43 of which are known or suspected carcinogens, and any of which are strong respiratory irritants. According to EPA, the basic components of mainstream smoke—i.e., smoke inhaled by the smoker—and secondhand smoke are similar. In some cases, in fact, secondhand smoke may even be more harmful.

Secondhand smoke is in the air in homes, work places, schools, restaurants, theaters, and public buildings. The Center for Disease Control tells us that 8 out of 10 nonsmokers report that they are annoyed by the smoking of others.

But there question we are considering here today goes beyond whether secondhand smoke is an annoyance to nonsmokers. We focus this morning on the level of health risks posed by secondhand smoke. We are going to examine the nature and degree of these risks as well as the assertions of some groups about scientific uncertainties or inaccuracies associated with EPA's calculation of these risks.

We will begin the hearing this morning with testimony from the Administrator of EPA, Carol Browner, and Surgeon General, Dr. Elders. I am particularly pleased to welcome the Surgeon General to her first hearing before this committee. While the words "public health" do not appear in the title of our committee, the laws we enact are designed first and foremost to protect the public health of the American people. I think this committee needs to hear more frequently from the Surgeon General. I hope this is the first of many appearances in which we will benefit from your testimony.

The Surgeons General of this country have been leaders in identifying the health risks of smoking. In 1965, the Surgeon General's Office issued its first warning about the health hazards of cigarette smoking and required a label to appear on every cigarette package. In 1972, the Surgeon General reviewed the health effects of secondhand smoke, and in 1986, a Surgeon's Report concluded that secondhand smoke can cause lung cancer in adult nonsmokers and respiratory infections in children of parents who smoke.

On March 21, 1994, just a couple of months ago, five former Surgeons General wrote:

> An overwhelming body of scientific evidence proves that environmental tobacco smoke poses a significant health risk for adults, children, and even the unborn. Many studies have shown that ETS is deadly.

The Environmental Protection Agency has also played a leading role in examining the health effects of secondhand smoke. In January of 1993, EPA issued a report on the respiratory health effects of secondhand smoke, which classified secondhand smoke as a known human or Group A carcinogen, a classification used only when there is strong evidence of a cause-and-effect relationship in humans between the substance examined and cancer. Only 16 other substances have been classified in this category.

The EPA report estimates that secondhand smoke is responsible for approximately 3,000 lung cancer deaths annually in nonsmokers in the United States and finds that infants and young children whose parents smoke are the most seriously affected by exposure. EPA estimates that passive smoking causes between 150,000 and 300,000 cases of bronchitis and pneumonia in infants and young children under 18 years of age each year, resulting in between 7,500 and 15,000 hospitalizations each year.

According to EPA, passive smoking can lead to a buildup of fluid in the middle ear, the single most common cause of surgery in children. EPA also estimates that between 200,000 and 1 million asthmatic children have their condition worsened each year by passive smoking, and that passive smoking can contribute to the development of thousands of new asthma cases in children each year.

While the EPA report only deals with the respiratory effects associated with secondhand smoke, both the American Heart Association and the American Medical Association have concluded that secondhand smoke causes thousands of deaths from heart disease each year. In short, according to these studies, hundreds of thousands of nonsmoking Americans are being denied their ability to protect their health and the health of their children because they happen to be, work, live, eat, or shop where others are smoking.

We will hear criticisms today about the scientific and statistical bases of EPA's conclusions. I intend to listen closely to these comments. The public has a right to expect the best scientific foundations for EPA's policies and actions. It is in that spirit that I look forward to the witnesses' testimony this morning.

I would yield now to my colleague from New Jersey, Senator Frank Lautenberg, for an opening statement.

OPENING STATEMENT OF HON. FRANK R. LAUTENBERG, U.S. SENATOR FROM THE STATE OF NEW JERSEY

Senator LAUTENBERG. Thank you very much, Mr. Chairman.

I very much appreciate your holding this hearing on the health effects of environmental tobacco smoke. The two bills I have introduced—S. 262 would prohibit smoking in Federal buildings and S. 1680 addresses prohibition in public facilities—seek to protect the American public against the dangers of secondhand smoke.

I introduced this legislation to continue progress already made toward a smoke-free environment, which started in 1987 when I wrote the law to ban smoking on airlines. Along with Congressman Durbin in the House, we authored the smoking ban that has since made virtually all domestic flights smoke-free.

Some detractors have sought to minimize this first step forward, but the airline ban introduced the segment of the public to the benefits and the comfort of a smoke-free environment. Since then, many localities have restricted smoking in various settings. Now it is time for the Federal Government to extend this protection to the non-smoking public in all public buildings.

Last weekend the New York Times sketched out in fascinating detail the unyielding posture of an industry which has continued to withhold research findings from the Government and to market products most people believe are responsible for the deaths of 400,000 Americans each and every year. Ignoring undisputed evidence, it is an industry that continues to insist publicly that cigarettes are neither hazardous nor addictive.

One wonders, what kind of evidence do they need? All kinds of smokers—and I used to be one of them—have told me about the number of times they wanted to quit. Some of them brag that they quit 50 times, but they started 51 times. That continues to persist. I don't know what it is going to take, but we listen to them as we hold this hearing.

As elected representatives of the people, the Congress has a responsibility to call the industry to task to perhaps regulate its products in the public interest and to protect the non-smoking public from involuntary exposure to a Group A carcinogen.

The Congress has moved toward this goal. This year, the legislation I sponsored called Pro–Kids, was finally enacted. It was enacted as part of an education objective. It requires virtually all federally funded children's programs to be smoke-free, including schools, day care centers, and community health centers. However, we have more work to do. We should make all public buildings smoke-free.

That is why I introduced the Smoke Free Environment Act with Congressman Waxman. This legislation would make all public buildings visited by 10 or more persons one day a week smoke-free. To the detractors of this legislation I say that if McDonald's and the Pentagon can go smoke-free, so can the Nation.

Mr. Chairman, each success in moving toward a smoke-free environment has faced the obstacles set up by a well-funded, tough, stubborn tobacco lobby at each step. The tobacco industry has consistently distorted the scientific research on environmental tobacco smoke and the purpose of my legislation. This morning I hope we will be able to set straight the record on environmental tobacco smoke.

Mr. Chairman, for those who can see this chart, a recent New York Times poll showed that 67 percent of all Americans favor a ban in smoking in all public places, which would be accomplished by enacting the Smoke–Free Environment Act. I have those results here. It is pretty dramatic. That is up, by the way, from 61 percent in 1991.

The American people want to breathe cleaner air. That is what this legislation would give them.

It is hard to figure out why people want to continue to ingest a substance which is a known carcinogen. And many smokers, as I said, will volunteer that they wished they had never started smoking and look for help in beating the addiction, an addiction that has been compared with the heroin addiction.

Later this morning we are going to hear from Mr. Christopher Coggins, a research scientist from R.J. Reynolds. He will be speaking for the tobacco industry and I look forward to hearing his testimony. He has a tough job ahead of him if he denies the evidence, as his industry has in the past, that demonstrates that tobacco smoke is addictive and dangerous to others.

Some of our most prominent scientists have found that smoking kills 400,000 persons per year. Our best scientists have found that environmental tobacco smoke is a Group A carcinogen, which causes 3,000 lung cancer deaths a year. The Congress and the country have an empirical basis for moving to establish a smoke-free environment for the American people.

My legislation is not about prohibition. If someone wants to smoke in the privacy of their own home, or even in their own car, or in their own yard, that is up to them. But it is about protecting those who choose not to smoke—nonsmokers—who suffer terribly from other people's smoking habit.

Mr. Chairman, once again I thank you for holding this hearing. If we are going to clean the air indoors, this is one excellent way to do it. I look forward to hearing the testimony from our witnesses.

Senator LIEBERMAN. Thank you, Senator Lautenberg.

Senator Faircloth?

OPENING STATEMENT OF LAUCH FAIRCLOTH, U.S. SENATOR FROM THE STATE OF NORTH CAROLINA

Senator FAIRCLOTH. Thank you, Mr. Chairman.

I hold a somewhat different view on this subject, but I want to thank the chairman for his holding the hearings and giving us an opportunity to present opposing witnesses and thought.

I am one of the few people—maybe the only one in the entire Congress—who spent a lifetime involved with tobacco in one phase or another. I grew up with it in agriculture and farming, so I am pretty familiar with it. But I have never smoked. I didn't run into the problem that you did, Senator Lautenberg. But I know every other thing about it that you can know except smoking.

But when I came to Washington, DC I learned a few things. One of the first things I learned was that common sense was in extremely short supply around here. It simply defies any common sense that I can come up with that we should ban the use of tobacco in virtually every place outside the private home based on a concocted study like the one we're going to hear about today.

And concocted it is. Senator Lieberman, you well said that it would be questioned, and it certainly is questioned.

In committee after committee, in hearings I have heard the same thing; Government studies concluding exactly what the bureaucrats wanted it to conclude. They decide where the place is and then they draw a road map that takes them there, despite a tremendous amount of information to the contrary.

In this particular case, EPA reviewed 11 different U.S. studies on the relationship between secondhand smoke and lung cancer—11 studies. Not a single one of those studies found that secondhand smoke was causing lung cancer—not a one of them. Yet EPA promulgated, by nitpicking the 11 studies, and came up with the conclusion that they did. They did it by lowering the level of confidence—they moved the goal post in the middle of the study to reach the conclusion they wanted to reach.

This is the only way they could take a variety of different studies, review them, and find something cumulatively that was not included in a single one of them. In other words, the sum became much greater than the parts.

Mr. Chairman, we have seen in recent weeks a feeding frenzy on an industry which employs hundreds of thousands of people in this country, many of them in North Carolina. In the House we saw the board chairmen of some of America's largest employers absolutely treated as if they were criminals.

I wonder whether we ought to place the witnesses under oath today and give them the same treatment that was accorded those men. The children from North Carolina are also going to be victims of tobacco when their parents' way of life is destroyed and they lose their jobs because the bureaucracy concocted a theory that they haven't been able to prove.

As I said, I have never smoked. But the time comes when you have to draw the line on the ridiculous kind of assumptions and so-called scientific evidence that the bureaucrats can dream up because they think it will please the politicians. That is exactly what we have. It is another power grab by the bureaucracy trying to penetrate deeper into the private sector to get into our private lives another round of rules, regulations, control of the private lives of the people of this country, another layer of bureaucracy, and another loss of freedom.

I think we need to stop where we are. I look forward to hearing what the witnesses have to say.

Senator LIEBERMAN. Thank you, Senator Faircloth.

We are honored to be joined by the ranking member of the committee and the subcommittee, Senator Chafee of Rhode Island.

OPENING STATEMENT OF HON. JOHN H. CHAFEE, U.S. SENATOR FROM THE STATE OF RHODE ISLAND

Senator CHAFEE. Thank you very much, Mr. Chairman.

I want to welcome the witnesses here today, and I want to thank you for having this hearing.

As you know, actual tobacco use has long been recognized as a major cause of health problems. That is no secret. It is a cause of lung cancer in humans, a substantial risk factor for heart disease, and it is responsible for over 400,000 deaths in our country every year.

In recent years, there has been great concern that nonsmokers may also be at risk as a result of their exposure to environmental tobacco smoke commonly known as secondhand smoke. Here is this report, which has been prepared by EPA, which I think is a significant one. I look forward to hearing the testimony on it today.

Mr. Chairman, I would ask that my statement be included in the record, but I would like to conclude by making the following comments.

As we all know, children are often at a greater risk from harmful chemicals due to a higher respiratory rate and due to the fact that their internal organs are still developing. So I think the EPA report does bear out—as I understand the explanation of it—and concludes that exposure to environmental tobacco smoke does increase the risk of lower respiratory tract and middle ear infections in children.

So Mr. Chairman, I think it is worthwhile for us to examine this. I would hope the witnesses would give particular attention to the effect on younger children.

Thank you very much, Mr. Chairman.

[Senator Chafee's statement follows:]

STATEMENT OF HON. JOHN H. CHAFEE, U.S. SENATOR FROM THE STATE OF RHODE ISLAND

Mr. Chairman, I would like to thank you for calling this hearing today to discuss the health effects of environmental tobacco smoke. I would also like to thank the Administrator of EPA and the Surgeon General for taking time out of their schedules to be with us today.

As you know, actual tobacco use has long been recognized as a major cause of health problems. A cause of lung cancer in humans, it is a substantial risk factor for heart disease and is responsible for over 400,000 deaths a year in the United States.

In recent years, however, there has been great concern that non-smokers may also be at risk as a result of their exposure to environmental tobacco smoke—commonly known as secondhand smoke. In response, in 1988, EPA undertook a massive effort, one I fully supported, to assess the respiratory health effects of passive smoking. The result is the document we have before us today, EPA's *Respiratory Health Effects of Passive Smoking*, which concludes that widespread exposure to environmental tobacco smoke presents a serious and substantial public health risk.

EPA further concludes that environmental tobacco smoke is a human lung carcinogen that is responsible for approximately 3,000 lung cancer deaths annually in non-smoking adults and Impairs the respiratory health of hundreds of thousands of children. The report also classifies ETS as a known human or Group A carcinogen. Fewer than 20 agents have been classified as Group A carcinogens.

This report is a powerful tool in the fight against harmful smoke emissions. I am hopeful that, by directing our efforts at providing information on the effects of ETS, we will make great strides towards preventing health problems before they occur. Our Nation spends billions of dollars each year on health care, unfortunately often after the fact. Many of the illnesses we experience, however, are preventable. In terms of public health, this report and its recommendations may provide us with a much-needed ounce of prevention, and help us to avoid the costly pound of cure in treating respiratory illnesses.

Over the last decade we have made considerable progress in abating some of the most harmful pollutants in our outdoor environment. Emissions from cars are no longer as injurious to air quality, and, under the recent amendments to the Clean Air Act, auto emissions will be reduced even more. Leaded gasoline, known to cause serious negative health effects in children, is being phased out. Once unsightly rivers are now returning to a state where they are fishable and swimmable.

Yet for all this progress, we have not turned our attention in a significant way to the air environment where Americans spend an average of 90 percent of their time: INDOORS. What's more, the threat posed by environmental tobacco smoke indoors may be heightened by the fact that many of us live and work in virtually airtight buildings. That is why I was so pleased to join the Majority Leader and Senator Lautenberg in authoring S. 656, the Indoor Air Quality Act which was approved by the full Senate last October. This bill will go a long way in providing the information necessary for home and building owners to deal with critical clean air issues.

Let me finish by highlighting a particular concern of mine with respect to tobacco smoke and indoor air pollutants generally, and that is the effect on our young people. Children, as we all know, are often at greater risk from harmful chemicals due to a high respiratory rate, and the fact that their internal organs are still developing. The EPA report bears that out and concludes that exposure to ETS increases the risk of lower respiratory tract and middle ear infections in children.

So, Mr. Chairman, I call on our witnesses, regardless of their particular interests, to remember our young people. The federal government must do everything it can to protect their well being and that includes prohibiting smoking in buildings utilized by children, which we did, through Senator Lautenberg's leadership, in the recently approved Goals 2000 legislation.

Mr. Chairman, the time has come to do away with the smoke filled room. Americans deserve better air quality, and I intend to work with you to make that a reality. Again I thank you for holding this hearing, and I look forward to the testimony.

Senator LIEBERMAN. Thank you, Senator Chafee.

Again, we are delighted that Administrator Browner and Surgeon General Elders have been able to be with us today. We look forward to their testimony.

We are going to run the timing lights in a 7-minute cycle, but if you haven't said some things that you think are important, don't feel that the lights constrict your First Amendment right to petition your Government.

[Laughter.]

Senator LIEBERMAN. Ms. Browner?

STATEMENT OF HON. CAROL M. BROWNER, ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

Ms. BROWNER. Thank you, Mr. Chairman and members of the subcommittee.

It is an honor to appear before you today to talk about a very serious issue; the issue of secondhand smoke, environmental tobacco smoke.

In January of 1993, the Environmental Protection Agency released an assessment of the respiratory health risks of passive smoke. Based on the total weight of the available scientific evidence, EPA concluded that the widespread exposure to secondhand smoke in the United States presents a serious and substantial public health risk. Mr. Chairman, cigarettes don't just kill people who choose to smoke; they kill people who choose not to smoke.

The EPA report has served as a turning point in this country, supporting the efforts of many people across this country who seek to protect those who choose not to smoke. It has provided the public, building managers, and Government officials with the knowledge that they need to take actions to protect the people of this country.

The EPA report found that environmental tobacco smoke is a human lung carcinogen, classified as a Group A carcinogen under EPA's carcinogen assessment scheme. The report concludes that secondhand smoke is responsible for approximately 3,000 lung cancer deaths each year in nonsmoking adults. Of these 3,000, the report estimates that approximately 2,200 are attributable to exposure outside the home.

Although the finding that ETS is capable of causing lung cancer in healthy adults is obviously significant, I have to tell you, Mr. Chairman, that as a mother of a young child I am personally very concerned about the serious effects on young children. Infants and young children whose parents smoke are at an increased risk of lower respiratory tract infections such as pneumonia and bronchitis. Children who have been exposed to secondhand smoke are also more likely to have reduced lung functions and symptoms of respiratory irritation such as cough, excess phlegm, and wheezing. In addition, passive smoking can lead to a buildup of fluid in the middle ear, the most common cause of hospitalization for children in this country for operations.

We also found that asthmatic children are especially at risk. EPA estimates that exposure to environmental tobacco smoke increases the number of episodes and the severity of symptoms for between 200,000 and 1 million asthmatic children every year. In addition, passive smoking is a risk factor for thousands of non-asthmatic children who develop the condition.

EPA firmly believes that the scientific evidence is sufficient to warrant actions to protect people from involuntary exposure to environmental tobacco smoke. Because of the health implications of exposure to environmental tobacco smoke documented in our risk assessment, EPA has recommended actions to help parents, decisionmakers, and building occupants prevent involuntary exposure to secondhand smoke. This is a brochure which we have provided to the public giving them simple answers to questions and telling them how they can protect themselves.

Our primary recommendations included in this brochure are that residents not smoke in their home or permit others to do so, particularly when young children are there; that every organization that deals with children—schools, day care facilities, other places where children spend time—have a smoking policy that effectively protects children from exposure to environmental tobacco smoke. In the work place EPA recommends that every company have a smoking policy that effectively eliminates involuntary exposure to environmental tobacco smoke either through complete bans or through limiting smoking to rooms that are specially designed to prevent smoke from escaping to other areas of the building.

Mr. Chairman, I might call the committee's attention to this report, "Developing a Smoking Lounge: Practical, Cost-Effective Ways to Accommodate Smokers". The recommendations in this report are identical to the recommendations made by EPA. I would note that this report is a product of R.J. Reynolds Tobacco Company. We have picked up their recommendations in terms of work place protections. If smoking is permitted in a restaurant or a bar, placement of smoking areas should take into account the ventilation characteristics of the space to minimize involuntary exposure.

Mr. Chairman, I take very seriously my responsibility and my Agency's responsibility to help educate the public about the hazards to health from secondhand smoke and actions they can take to prevent involuntary exposure. That is exactly what we have attempted to do here. That is what the scientific study we conducted suggested was appropriate.

I know there are a number of particular questions about the basis for our study, but I would like to make a few brief comments about that study.

The report was issued under the authority of the Radon Gas and Indoor Air Quality Research Act of 1986, which directs EPA to conduct research and disseminate information on all aspects of indoor air quality. The report summarizes the findings of the Agency's extensive investigation of the respiratory health risks from exposure to environmental tobacco smoke. It incorporates comments and recommendations from the public as well as two reviews by EPA's Science Advisory Board, a panel of independent scientific experts in this field. There were 18 individuals chosen, scientists from across the country with expertise, to review the findings of the Agency.

The Science Advisory Board unanimously endorsed both the conclusions of the report and the methodologies employed. The Department of Health and Human Services has endorsed the report and the National Cancer Institute within HHS has printed it as one of its series of scientific monographs.

Mr. Chairman, I would also like to speak briefly to the bills that I know are being considered and then answer questions that you may have on them specifically.

The Smoke–Free Environment Act of 1993, S. 1680, as we understand it, would prohibit smoking of tobacco products within any building regularly entered by 10 or more persons at least one day per week, including Federal, State, and local government buildings. We believe that passage of S. 1680 would provide comprehensive protection from involuntary exposure to environmental tobacco smoke in indoor environments for all persons including children, workers, and the general public.

We also believe that there are a number of important secondary benefits associated with the passage of that bill. First, studies indicate that smoking restrictions in some cases can help encourage those who do choose to smoke to quit or cut back and discourage nonsmokers from starting. In addition, Federal legislation in this area we believe would help level the playing field for businesses that are concerned about any potential competitive disadvantage that could result from strong local smoking restrictions.

I think it is very important to note that S. 1680 would not attempt to control individual behavior in the home, nor would it prohibit people who choose to smoke from doing so at most outdoor locations or in buildings that provide properly designed smoking rooms. We think this is appropriate.

We support this bill and we do look forward to working with the subcommittee and the Members of the Senate in addressing any specific concerns as the bill moves forward.

The second piece of legislation, S. 262, Preventing our Federal Building Workers and Visitors from Exposure to Deadly Smoke Act of 1993, would establish smoking policies in all federally owned or leased buildings. The general thrust of that bill represents responsible Government action for protecting public health and provides a model for State and local governments to follow.

Again, Mr. Chairman, smoking is one of the most dangerous causes of illness in this country. And it is also one of the most preventable. Smoking restrictions would reduce premature deaths among smokers and nonsmokers. They would improve health, especially the health of the children of this country, resulting in fewer cases of respiratory illness, ear infections, and asthma.

We believe that we have a responsibility to protect those who choose not to smoke and we are happy to answer any questions regarding the scientific study and the recommendations that have been made by the Environmental Protection Agency.

Senator LIEBERMAN. Thank you, Ms. Browner.

Dr. Elders, again, welcome. We look forward to your testimony.

STATEMENT OF HON. M. JOYCELYN ELDERS, M.D., SURGEON GENERAL, UNITED STATES PUBLIC HEALTH SERVICE

Dr. ELDERS. Thank you, Mr. Chairman and members of the Subcommittee on Clean Air and Nuclear Regulation.

First of all, I want to thank you for inviting me to this hearing to address the problem of environmental tobacco smoke on health. In February, I had the pleasure of appearing with five of the former surgeons general before Chairman Waxman on this issue, the health consequences of environmental tobacco smoke. Each one of the previous surgeons general cited the extensive science base that supports one undeniable fact: environmental tobacco smoke is a very real environmental hazard, particularly to our most vulnerable citizens, our children.

Today, I am equally pleased to be here to applaud the efforts to bring this issue to the Senate. Your efforts on this bill—and Senator Lautenberg, your efforts on the recently enacted Pro–Kids provision of the Goals 2000 Educate America Act—will do more to protect our children than many of the other things we can do. I want to thank you for that.

Now let me turn to the issue at hand.

Picture with me for a moment a room full of preschoolers, each with a cigarette in their mouth. In essence, this is what we are doing to our children every time we expose them to secondhand smoke. It has toxic and carcinogenic effects that are very similar to mainstream smoke.

When we smoke around our children, our children are smoking. Not only are our children more vulnerable, as you have heard from Administrator Browner, but they are also more vulnerable because children are held captive to adult management of their space. Unlike adults, they cannot negotiate for smoke-free environments. And unlike adults, they cannot simply get up and leave.

You have heard the facts reviewed, but I would like to review them again because I think they are so critical.

Mr. Chairman, 9 million American children under the age of 5 are exposed to secondhand smoke in their homes every day. Nearly 800,000 children in the United States are exposed to secondhand smoke in their child care centers or at school. Many other children are forced to breathe air polluted with cigarette smoke in automobiles, shopping malls, and restaurants, particularly fast-food restaurants that cater to children.

Exposure to secondhand smoke causes up to 300,000 lower respiratory tract infections each year in children less than 18 months of age. These needless infections result in up to 15,000 hospitalizations yearly. Environmental tobacco smoke is a known risk factor for asthma and causes increased severity in children with asthma and we have more than 4 million children in America that have asthma.

In January of 1993, environmental tobacco smoke was classified as a Group A carcinogen. These are carcinogens for which no safe level of exposure have been established. An estimated 3,000 lung cancer in health nonsmokers are caused each year by environmental tobacco smoke. In recent months, as you know, several fast-food restaurants, most notably McDonald's, have gone smoke-free. The concentration of secondhand smoke in these establishments are places where our children eat, play, and work is alarming.

Restaurant workers have a 50 percent to 90 percent increase in lung cancer risk due to their exposure to secondhand smoke. We must make sure that every parent in this country is aware of these facts, as no parent would willingly expose their child to any danger, and secondhand smoke is undeniably a danger.

Secondly, we must make sure that all of our citizens know that environmental tobacco smoke is a cause of disease, including lung cancer in health nonsmokers. We must teach our children and our school—as your child reminded you, Senator—about the dangers of smoking and environmental tobacco smoke. We know that children who have had one lecture on the hazards of smoking—you can reduce cigarette smoking 30 percent. Many of our children do not even get this one lecture. We must pass rules and regulations to protect the health of all our citizens.

Today, we stand with the findings and the even stronger findings of EPA that clearly document the deadly health consequences of environmental tobacco smoke. Today, I again join Administrator Browner in supporting S. 1680, the Smoke-Free Environment Act of 1993, and we look forward to working with the subcommittee over specific concerns as the bill is debated.

I look forward to working with the Senate to protect the public from this enormous and unnecessary health risk, particularly the health of the most valuable resource we have in our country, our children, from the health hazards of the increased irritation of their eyes, ears, noses, and throats from environmental tobacco smoke, from the irritation of their lungs resulting in increased pneumonia, increased asthmatic attacks, increased wheezing, and from the increase risk of lung cancer, and we look forward to your health in making this a real possibility for all of our citizens.

Thank you.

Senator LIEBERMAN. Thank you, Dr. Elders. I appreciate your statement and Administrator Browner's.

I think you have appropriately focused on the subject of this hearing. There has been a lot of discussion in the news lately—mostly coming out of Chairman Waxman's committee on the tobacco industry and past practices of that industry. This hearing really is focused on the two bills that are before us that would regulate the access that secondhand smoke would have to nonsmokers, and in that sense to deal with the scientific basis for doing that.

Both of you have endorsed both of these bills that are before us. I note that for the record. Those are significant endorsements.

You have heard Senator Faircloth today refer to this study as concocted and also saying that you moved the goalpost in the middle of the study in terms of the combining of the various studies that you looked at. I wonder if you could first go into a little bit of detail on the methodology of how this study was carried out. I know the report is based on an assessment of other studies that were done. I wonder if you would describe that in general terms. I am sure Senator Faircloth will be more detailed, but I would like you to respond to some of the allegations he has raised in his opening statement.

Ms. BROWNER. Mr. Chairman, the study undertaken by EPA has been widely recognized as comprehensive. More than 30 other studies were reviewed in reaching the conclusion that environmental tobacco smoke is a Group A carcinogen. We base that conclusion on the way——

Senator LIEBERMAN. I apologize for the interruption, but just I have been through this enough to know that denoting secondhand smoke as a Group A carcinogen is a significant conclusion. Could you dwell for just a moment on what that means?

Ms. BROWNER. I think the Surgeon General said it well in her comment, which is that there is no safe level of exposure. That is what we mean when we categorize something as a Group A carcinogen. It is a classification that is used in only very limited circumstances by the Environmental Protection Agency. Environmental tobacco smoke I believe is the 16th Group A carcinogen, something given that status by EPA.

I might also note that it is the only one on the list over which EPA does not have regulatory authority. In no way do we claim to have that authority. Rather, we believe we have a responsibility to educate the public when the weight of the evidence shows there to be a real problem.

Senator LIEBERMAN. We are saying that there is no safe level of inhalation of secondhand smoke. That doesn't mean that anyone who inhales any secondhand smoke is going to get cancer.

Ms. BROWNER. No. It means that in the studies that were reviewed—and these are studies done over an extended period of time—that led to EPA's conclusion, which has been scientifically peer-reviewed outside of the Agency—the weight of the evidence showed real effects in people who choose not to smoke when they are exposed to secondhand smoke. There were 17 studies which looked at exposure level. All 17 of those studies showed an increased risk at the highest exposure levels.

We do have a chart that might be helpful for the committee in explaining the science that was used here. I think it would also be helpful to note, Mr. Chairman, that the methodology used by the Agency was also reviewed by the scientific advisory panel at EPA—both the methodology and the conclusions—and in both cases they found them to be correct and to be appropriate.

The first chart shows what I refer to as the weight of the evidence. In terms of all the issues and the studies that were looked at, when taken in their entirety, the weight of the evidence justifies classifying environmental tobacco smoke as a known human Group A lung carcinogen.

In the second chart what you see are the 30 epidemiological studies that the Agency reviewed. It shows that in each instance the analysis of individual study—24 out of the 30 studies that we reviewed showed an effect. The probability of that occurring by chance is the number that appears across the bottom, for example, 1 in 10,000; 1 in 10 million; 1 in 1 billion. So the likelihood that these studies reflected something that was mere chance is not an appropriate reading of the report.

Senator LIEBERMAN. Why don't you tell us, if you can, how the 30 studies were chosen? I don't know that this is a charge, but I would suppose that somebody who was questioning the results might say that the studies were preselected so that they would show the outcome you wanted to show.

Ms. BROWNER. The studies that were looked at generally focused on exposure in the home for the reason that it is easier to control for changes. In a work place, people change office mates, they change buildings, they change jobs—a lot of things get changed. So the majority of the studies that were looked at focused particularly on the wives of smokers. The 30 studies that were chosen were reviewed by the scientific panel in terms of presenting a balanced view.

I might say that 24 of the 30 studies chosen—6 did not but not 24 did—find an increased risk of lung cancer in people who choose not to smoke. We then decided that of those studies nine of them were statistically significant. So you start with the universe and then you begin to narrow it down in reaching your conclusions.

Senator LIEBERMAN. But I assume that these studies were randomly selected. In other words, your folks didn't just go and look for studies that you thought were done by people who were against smoking.

Ms. BROWNER. I think that is the right laymen's term to use.

Senator FAIRCLOTH. I didn't hear the answer.

Senator LIEBERMAN. I believe the answer was yes, that the studies were not preselected—in other words, they weren't just choosing ones that would come to the result they wanted to come to, that these were more or less randomly selected.

Ms. BROWNER. Let me be more precise, Mr. Chairman.

Senator LIEBERMAN. Go ahead.

Ms. BROWNER. The 30 studies represented all of the scientific studies that existed at the time that EPA commenced its analysis. So we were not excluding scientific studies. We weren't picking through scientific studies—as I think some have suggested—to find ones that would support the outcome. Rather, we looked at all of them and then there was an analysis done to determine which of those were statistically significant. Then we show the probability of occurrence by chance of those being statistically significant. We then make our conclusions based on those which are statistically significant. But all studies existing were looked at.

I know there will be questions asked, as in the past, about studies that were concluded after the EPA analysis was undertaken. The question has been asked, Why weren't those studies put into the original list of studies?

The answer is simple. They weren't available. They hadn't been subjected to the scientific peer review. They were not completed in time. Therefore, it was not appropriate to include them. The one that gets a tremendous amount of focus is the Brownson Study. I think if you look at the conclusions Dr. Brownson reaches and compare those to the conclusions reached by EPA, they are similar.

Senator LIEBERMAN. Dr. Elders, let me ask you one question before my time is up.

In supporting the legislation before us that would effectively ban smoking in public places, I assume you are reaching a conclusion from a public health point of view that the existing law and practice is not adequate to protect public health.

Let me focus on one experience that all of us have had, which is to go into the restaurant and to be asked whether we want to sit in the smoking or nonsmoking section.

I thought you had some interesting and powerful numbers on the restaurant workers. But do you reach the conclusion that if I choose to sit in the nonsmoking section with my family, as I do, that I am not adequately protected from smoke in a restaurant?

Dr. ELDERS. That is correct, Mr. Chairman.

Just because you are sitting in a different spot does not really protect you. If people put in specially ventilated rooms that are ventilated to the outside and where the smokers are closed off, that might be adequate. But of course, most restaurants do not have or offer that kind of facility. Very few work place sites offer that kind of building now.

Senator LIEBERMAN. What is the basis for the number you quoted? Is there a study on restaurant workers? I think you said that there was a 50 to 90 percent increase.

Dr. ELDERS. Yes, there is, Mr. Chairman. I will have to get that data for you. There is a study looking at people who have worked in restaurants for a long period of time versus people who have not worked in restaurants that say that there is an increased risk.

Senator LIEBERMAN. And it is lung cancer? Is that right?

Dr. ELDERS. Yes, sir.

Senator LIEBERMAN. Thank you. That is the end of my first round.

Senator Faircloth?

Senator FAIRCLOTH. Thank you, Mr. Chairman.

My first question would be to Ms. Browner.

The Brownson Report, which you very lightly alluded to, was funded by the National Cancer Institute. It reported overall most significant increase in risk of cancer or lung cancer by secondhand smoke. Is that not right?

Ms. BROWNER. I would actually——

Senator FAIRCLOTH. Have you read the report all the way through?

Ms. BROWNER. No, I have not read every report, but——

Senator FAIRCLOTH. Then how can you discuss it?

Ms. BROWNER. Senator, I might say that my staff has reviewed——

Senator FAIRCLOTH. But your staff isn't here to testify. You are.

Ms. BROWNER. I would be more than happy to bring them up, if you would like.

Senator FAIRCLOTH. I am sure they would be glad to come, but now tell me about it.

Ms. BROWNER. I think it is important to note that Dr. Brownson, in his own study—and this is a quote from the author's own conclusion in the addendum—says:

> Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking.

I would also note that the Brownson Study was completed essentially at the same time as EPA was completing its study. However, since it had not been included in the EPA study because it had not been completed when we commenced the study, we did go back and look at that study, and I think two or three other studies, that were also completed after the EPA findings were issued. Based on our review—we looked at them taken in their entirety—it would not be appropriate to find that they would change the outcome of the Group A carcinogen designation for secondhand smoke.

Senator FAIRCLOTH. When did EPA become aware of the Brownson Study?

Ms. BROWNER. To my knowledge, Senator, EPA had been aware of the Brownson Study for some time because as they were looking at these issues they were familiar with the fact that another study was underway. But again, the study was not completed.

Senator FAIRCLOTH. When you found out about the Brownson Study, did you consider delaying the release of your report in order to include the Brownson Study, or did you speed it up so that you wouldn't have to include it?

Ms. BROWNER. The final assessment that was issued by EPA does include a brief discussion of the Brownson Study in an addendum attached to the report.

Senator FAIRCLOTH. Of these 11 reports that you studied, not a single one indicated the conclusions that you came to by promulgating the 11 with the people from EPA. I believe you said you had 18 people to look at it.

Ms. BROWNER. The scientific peer review panel was made up of 18 individuals, all of whom found the EPA report to be valid both in terms of the methodology and the conclusion.

Senator FAIRCLOTH. Who selected them?

Ms. BROWNER. The EPA has a scientific advisory panel.

Senator FAIRCLOTH. Who are the selected 18 people?

Ms. BROWNER. Senator, these are well-recognized experts from across the country. They are not selected by EPA staff.

Senator FAIRCLOTH. I didn't ask you their credentials. They were selected by the EPA.

Ms. BROWNER. Absolutely not. They were selected by the science advisory panel, which are——

Senator FAIRCLOTH. Who paid them?

Ms. BROWNER. The science advisory panel are experts who advise EPA. They are not on the payroll of EPA. They advise EPA on a number of scientific issues. They come from across the country. They are people in academic institutions, in hospitals; they are recognized experts in their fields. They worked to put together the panel of 18 experts that reviewed these reports.

Senator FAIRCLOTH. Ms. Browner, if you would please be brief, who paid the 18 people?

Ms. BROWNER. Their travel may be paid by EPA, but their salaries are not paid by EPA.

Senator FAIRCLOTH. There has been a number of other carcinogens that cause cancer and there are many, many of them, such as electromagnetic waves from power lines. On the scale that you used denoting causes of cancer and other problems—you say that anything below a two is insignificant. We come back and see that this tobacco study was a 1.9. We find that electromagnetic waves are a three. Are you following me?

Ms. BROWNER. Senator, I believe you may be referring to electromagnetic fields.

Senator FAIRCLOTH. Yes.

Ms. BROWNER. EPA has not made a finding that electromagnetic fields are a Group A carcinogen. We would be more than happy to submit for the record the list of those things that have been found to be Group A carcinogens.

I might note that they are things like arsenic, benzine, chromium, nickel, radon—not electromagnetic fields.

Senator FAIRCLOTH. Have you checked the electromagnetic waves? The reports we have is that that is a three on a scale of one to ten and tobacco is a 1.9.

Ms. BROWNER. Senator, the Agency is involved in a comprehensive study of electromagnetic fields and the effect on the public. We have not concluded those studies.

Senator FAIRCLOTH. The study I have been reading puts it at a three now, so that is going to present it as a much more dangerous thing than the tobacco smoke.

Ms. Elders, don't you think it is becoming excessively intrusive into the private sector when we talk about a Federal law forbidding people from smoking a cigarette in a place of business?

Number one, do you think it is enforceable? Prohibition didn't work. They went in and got a drink. I think you have first-hand evidence that drug enforcement has been pretty feeble. So what do you think is going to be the effectiveness of this? Are we going to drag everybody into Federal court and how many judges will it take?

Dr. ELDERS. Senator, you have never heard me say that we should prohibit tobacco smoke. I feel very strongly that we should educate our young people. We should not allow our young people to be exposed to environmental tobacco smoke.

Senator FAIRCLOTH. So then you are not supporting the bill that says that it is outlawed in places where 10 people go into a day?

Dr. ELDERS. I feel that we should not allow other people to be exposed to tobacco smoke. There is a difference in banning smoking. You can smoke in your home and your car.

Senator FAIRCLOTH. I said my business. You didn't hear my question. I own a business. Are you saying that is a good law to put on the books and that we can enforce that?

Dr. ELDERS. I feel that is a good law to put on the books. I think most parents——

Senator FAIRCLOTH. You said that you don't know whether it is or not?

Dr. ELDERS. No, I said that I feel that that would be a good law.

Senator FAIRCLOTH. How do you enforce it?

Dr. ELDERS. It is your business. If it is the law, you as a businessman will abide by the law.

Senator FAIRCLOTH. Has that been true of the drug dealers?

Dr. ELDERS. Sir, we have a lot of laws that we break all the time. That is why our prison system is so huge. But just because people break the law does not mean that it is not a good law.

Senator FAIRCLOTH. In other words, just go ahead and put the laws out there. We can't enforce them. We just roll them out. They really don't have any effect. But it sounds good for the politicians and the bureaucrats to say that we passed a law even though it is totally and completely unenforceable.

Dr. ELDERS. Sir, we have 435,000 people who die every year related to tobacco smoke. We enforced it on airplanes and we all thought it would be a problem. But every time we get on an airplane, they remind us that we cannot smoke on that airplane. So I feel that we should not allow people to smoke in public places.

Senator FAIRCLOTH. I read these dramatic figures that are readily concocted by governmental agencies to fit whatever program. You all can cut a set of figures to fit anything you want to be impressive with.

Which do you consider the most dangerous detriment to the country today, drugs or tobacco smoke?

Dr. ELDERS. Sir, if you really look at the number of people who die, there is no question that tobacco caused more deaths than drugs or alcohol.

Senator FAIRCLOTH. That is a very good answer.

Is that the reason you recommended legalizing drugs?

Dr. ELDERS. Sir, I did not recommend legalizing drugs.

Senator FAIRCLOTH. What did you recommend?

Dr. ELDERS. I recommended that we study the issue and find out what is best for us to do. I still feel that we need to study what we need to do about the drug issue because it is a real public health problem in our country.

Senator FAIRCLOTH. If you didn't recommend legalizing it, you sure got branded with it.

Senator LIEBERMAN. Thank you, Senator Faircloth.

We will do another round, at least, if you have further questions.

Senator Lautenberg?

Senator LAUTENBERG. Thank you very much, Mr. Chairman.

This I assume is the report we are talking about.

Who is this bureaucrat, Dr. Samuel Broder, director of the National Cancer Institute?

Dr. ELDERS. He is the bureaucrat who runs this country's National Cancer Institute.

Senator LAUTENBERG. So he endorsed this?

Dr. ELDERS. Yes.

Senator LAUTENBERG. This bureaucrat says:

> It is extremely unlikely that any other product known to harm the consumer when used as intended is also known to harm adults and children subjected to involuntary exposure would be so tolerated by society. Thus, while the practice of smoking may be a legal one, information in this report makes it clear that smokers have a responsibility to ensure that their behavior does not jeopardize the health and well-being of others.

He criticizes an industry that would not attempt to protect the people that it is harming out there.

We had a discussion about whether or not one carcinogen was worse than another and whether one way to kill people was worse than another. We know that cars kill people when driven at excess speeds, when driven carelessly, when driven under the influence. We don't ban cars. We ban speeding, drunk driving, et cetera.

I think what we have to do is once and for all try to dispel the notion that this is some kind of a trumped up statistical exercise that is designed just to harass people.

I understand my colleague and friend from North Carolina wanting to protect jobs. The tobacco industry, with all the creativity that it has, the marketing capacity, and the money that it makes, could find another way to get these people employed through retraining. It is like the defense industry; at some point the reason for existence gets challenged. The asbestos companies out of business. People lost jobs, but the lost their jobs because people lost their lives. That is why we did it. We have to protect the public health. The larger issue is: how do we protect our citizens?

It is pitiful to see people lose jobs no matter where or when they lose them or for whatever reason. We have to try to see if we can help them convert.

Ms. Browner, I understand that there are 16 Group A carcinogens. EPA calls these substances Group A carcinogens because there is epidemiological evidence that they are dangerous to humans. Of these 16, how many are not regulated by EPA?

Ms. BROWNER. The only one that EPA does not have specific regulatory authority over is environmental tobacco smoke. I might also mention, Senator, that environmental tobacco smoke is the only Group A carcinogen for which the cancer risk in humans was detected at environmental exposure levels rather than occupational or pharmaceutical levels.

Senator LAUTENBERG. As both of you know, many private companies have gone smoke-free since EPA issued this report in 1993. McDonald's and Taco Bell—talk about guts, for McDonald's to stand up there with its exposure and with its traffic and say that you can't come in here smoking—they are not telling people not to smoke. They are saying that in this place where there are lots of kids, you cannot smoke. You are not allowed to jeopardize the health of these children.

How many Americans, therefore, are still exposed to environmental tobacco smoke?

Ms. BROWNER. We estimate that 23 percent of the population today is covered by smoking restrictions in the work place. For the remainder of people who work outside of their home there is exposure, particularly because in most of our modern office buildings you have integrated ventilation systems. So even though you may not be on a floor where smoking is occurring or in a part of the building where smoking is occurring, that air is being recirculated constantly so there are exposures that can occur.

Senator LAUTENBERG. Could you tell me how many lives this Smoke–Free Environment Act might save each year if it were enacted into law?

Ms. BROWNER. We estimate 3,000 to 4,000 lung cancer deaths a year to be associated with secondhand smoking exposure .

Senator LAUTENBERG. That is environmental tobacco smoke. I asked the broader question, Ms. Browner, of how many lives overall—Dr. Elders?

Dr. ELDERS. It is estimated that it is 434,000 deaths per year that are related to tobacco smoke.

Senator LAUTENBERG. And if we enacted the Smoke–Free Environment Act, that might take a portion of those deaths and eliminate or at least reduce the possibility of these. How many might that be? Do you have any idea?

Ms. BROWNER. The work that we have done, Senator, shows that obviously if you ban smoking in the public places or allow smoking only in separately ventilated rooms, you are clearly protecting those people who choose not to smoke. In terms of the individuals who have chosen to smoke, in many instances the evidence suggests that there will be a decrease in the number of cigarettes they smoke in any given day. That will obviously have positive health benefits associated with it.

Senator LAUTENBERG. Are you familiar with the Smoke-Free Environment Act that was put into law in New Jersey?

Ms. BROWNER. Yes.

Senator LAUTENBERG. What would be the benefits of the Smoke–Free Environment Act be to the State of New Jersey?

Ms. BROWNER. We did an analysis of the State of New Jersey based on the population compared to the population of the rest of the United States. We assumed in New Jersey that 23 percent of the population is currently covered by comprehensive smoking restrictions, which is what we find across the country.

We found that the benefits of smoking-restrictive legislation comparable to S. 1680 would be $1.2 billion to $2.2 billion per year in the State of New Jersey.

Senator LAUTENBERG. The bill I call Pro–Feds, which is the one that makes all Federal buildings smoke-free, passed the Senate last year and was dropped in Conference. Now the House of Representatives passed a similar measure by a voice vote.

If Congress passed this bill, would it cost the Government additional funds, or might it save us some money?

Ms. BROWNER. We actually believe there are savings associated with that legislation. The major savings would be between $108 million and $258 million per year for the Federal budget. Those savings are a result of reduction in housekeeping and maintenance expenses. We also believe that there may be additional savings in fire property damage and reduced absenteeism. If you include all of these the savings would be on the order of $100 million to $300 million per year.

Senator LAUTENBERG. What is the estimated cost to society to this country for smoking?

Ms. BROWNER. For smoking? Not just for secondhand smoke?

Senator LAUTENBERG. No, for smoking overall.

Dr. ELDERS. It has been estimated that the increased health care cost is $69 billion.

Senator LAUTENBERG. Does that consider the productivity lost?

Dr. ELDERS. I don't think so, Senator. That is just for the increased health care costs.

Senator LAUTENBERG. Some critics of the EPA report, including Dr. Jane Gravelle of CRS, have argued that there is a threshold for environmental tobacco smoke before it is harmful to a nonsmoker.

Is this true? Or is any exposure to environmental tobacco smoke dangerous, to children, particularly, with respiratory disease?

Ms. BROWNER. The concept of threshold is a complicated one and is one that deserves the attention of the experts that will come after us. But it has to be answered separately when you look at cancer versus the non-cancer effects. Obviously, the effects in children we are seeing are non-cancer effects.

Any time you discuss a threshold, there is obviously the phenomenon of individual susceptibility that come into account. So some people are at a heightened threshold and others are at a lower threshold. Smokers vary in sensitivity. Nonsmokers may be more prone to the effects of smoke than those who have chosen to smoke. For children and people who already have respiratory ailments, there may be a heightened sensitivity; in the case of asthma, for example.

This is a complicated area and there is not a bright line that is appropriately drawn.

Senator LAUTENBERG. The age group of children that are most affected are what, Dr. Elders?

Dr. ELDERS. The young children. The younger the children, the greater the effect.

Senator LAUTENBERG. Up to 18 months?

Dr. ELDERS. Up to 18 months is where we think the greatest effect is.

Senator LAUTENBERG. Mr. Chairman, are we going to go around again?

Senator LIEBERMAN. We will do another round, if you would like.

Thank you, Senator.

Ms. Browner, let me come back to the perspective of the subcommittee on clean air and the focus on indoor air. I said in my opening statement that EPA had ranked indoor air pollution as one of the top four threats to the health of the American people. Talk a little bit about that and put the secondhand smoke question we are considering within that discussion.

We have become accustomed over the years to think of air pollution as the smoke stacks and the car exhaust systems, but clearly, we spend most of our time inside. So it may be that indoor air will have a greater effect on our health than outdoor air. How significant a part of indoor air pollution is smoking?

Ms. BROWNER. In looking broadly at environmental problems and environmental risks, EPA has found indoor air to be a very real risk. The issue of smoking as it relates to indoor air is a significant component, particularly in those places where we have not seen actions taken.

I think it is important to understand that what distinguishes secondhand smoking exposure from other risks that we deal with at EPA is that this is clearly preventable. For people who chose not to smoke, their rights need to be respected, they need to be protected, and that is what the recommendations we have made are all about. It is protecting those people who have chosen not to smoke.

Senator LIEBERMAN. When you say "preventable" you mean as compared to other elements of indoor air pollution?

Ms. BROWNER. When you look at all the elements of indoor air pollution, it is a complicated science. This is one of those that is easily prevented. Others are preventable, but the solutions may be more complicated. This one is easily prevented.

Senator LIEBERMAN. Let me go back to some of the science here which relates to what you just said.

The EPA's conclusion that secondhand smoke is a human lung carcinogen is based on evidence that suggests that secondhand smoke is chemically similar to so-called mainstream smoke, the smoke that is inhaled by smokers. Some critics have argued that secondhand smoke is not chemically similar to mainstream smoke since it is inhaled in a different manner, it burns at different temperatures, and it is presumably less concentrated than mainstream smoke.

How would you counter the criticism that is directed at the evidence that suggests that secondhand and mainstream smoke are in fact chemically similar?

Ms. BROWNER. I think if you look at the studies that we looked at, if you look at what we found in those studies in terms of the lung cancer deaths, the respiratory effects—what we see is real human health consequences from exposure to secondhand smoke.

I think people can spend a lot of time arguing about this or that scientific report. I don't think it is fair to say that EPA didn't undertake a comprehensive analysis when we looked at every single report that was available at the time of our work. All 30 reports that were available in the scientific community were reviewed.

Senator LIEBERMAN. Let me go back to the Brownson Study, which Senator Faircloth talked about, that has been the subject of criticism because it was not included in the EPA report.

I am paraphrasing, but I think it is fair to say that you said that the Brownson Study showed that there were small but consistent increases in lung cancer. So if the Brownson Study were included in EPA's report, would it have changed the conclusions of the report?

Ms. BROWNER. No, we do not believe that it would have changed the conclusions of the report. In fact, we looked at not just the Brownson Study but several other studies on this issue which were completed after EPA had begun its work. In looking at all of those, we found no reason to change the conclusions of our determination that secondhand smoke is a Group A carcinogen.

Senator LIEBERMAN. You held up some brochures and pamphlets earlier, one of which I gather was produced by the tobacco industry.

Ms. BROWNER. That's correct.

Senator LIEBERMAN. Is that the one developing a smoking lounge?

Ms. BROWNER. Yes.

Senator LIEBERMAN. And the other is EPA's series of recommendations?

Ms. BROWNER. Right.

Senator LIEBERMAN. Obviously one of the things, among many, that this subcommittee and the full committee and Congress will consider—particularly those that would ban smoking in all public places—is the cost of implementing and the ease with which these can be implemented. I wonder if either yourself or Dr. Elders can comment on that, particularly taking off from the smoking lounge idea.

I gather what we are saying is that there is no safe way to separate them. The premise is that there is no safe way to separate smokers from nonsmokers in the same enclosure. To be safe, you either have to ban smoking for the building altogether or create a separate location with a separate ventilating system, a separate room essentially.

So we are always making cost/benefit calculations. The question I would have is whether there is any sense you can give us of how much this would cost in relationship to the benefits you have described.

Ms. BROWNER. If it is okay with you, Mr. Chairman, I might just briefly quote from this document distributed by R.J. Reynolds in which they say:

> Developing a smoking lounge need not be expensive or difficult. In many cases, existing rooms or offices can be converted into a smoking lounge with very little time, effort, or money. Smoking lounges can also easily be incorporated into new construction by following a few guidelines.

This then goes on to make recommendations as to what is a proper ventilating system for existing rooms. It is a very good document. It is very comprehensive in its recommendations. There are even diagrams as to how you would actually do it in a room of one size and then for a larger room. I think it is fair to say that people who have looked at these issues—including the Building Owners and Managers Association—have found that these kind of rooms can be created within existing structures for a reasonable cost.

Senator LIEBERMAN. Dr. Elders, do you have anything to add to that?

Dr. ELDERS. No, sir.

Senator LIEBERMAN. I have no further questions.

I yield to Senator Faircloth.

Senator FAIRCLOTH. Thank you, Mr. Chairman.

Ms. Browner, why did EPA, right in the middle of the reassessment process, relax and change the normal standards of confidence interval from 95 percent to 90 percent. Why did you lower it?

Ms. BROWNER. Senator, a confidence interval is the degree of certainty, the possibility that the effect did not occur by chance.

Senator FAIRCLOTH. I know what it is.

Ms. BROWNER. There are two different statistical methods that were used. In one instance, it was a two tail and in the other instance it was a one tail. Both of these methods were reviewed by the scientific peer review panel and found to be appropriate. EPA has used one tail in other instances, for example, cadmium nickel, methyl chloride. These are valid and appropriately used statistical tools.

Senator FAIRCLOTH. Did you lower the confidence interval from 95 percent to 90 percent? Just answer it yes or no, please.

Ms. BROWNER. That is not a yes or no question. I apologize, but it is not. This is a complicated area of the science and I am more than happy to explain it.

Senator FAIRCLOTH. Then is this a true statement? We did not lower it from 95 percent to 90 percent.

Ms. BROWNER. Our methodology has been reviewed and approved by people who are recognized experts in this field across the country.

Senator FAIRCLOTH. All right. Thank you.

Is it true that before EPA changed the confidence interval, not one of the U.S. lung cancer studies reported a significant increase from secondhand smoke?

Ms. BROWNER. We didn't change the confidence interval.

Senator FAIRCLOTH. You did not change it?

Ms. BROWNER. We did what is scientifically appropriate. I have a chart and I am more than happy to explain what we did.

Senator FAIRCLOTH. But is it true that before it was changed—and it was changed——

Ms. BROWNER. What we did was scientifically valid.

Senator FAIRCLOTH. I am confident of that. No doubt.

But not one of these 11 U.S. lung cancer studies reported a significant increase from secondhand smoke before you changed the methodology. Isn't that right?

Ms. BROWNER. Let me call your attention to the 17 of 17 studies, which were characterized by exposure levels.

Senator FAIRCLOTH. I am talking about the 11.

Ms. BROWNER. The issue you are referring to, the statistical, analytical methodology used by the Agency was used only in this one column of meta-analysis. It was found to be appropriate. That is one piece of the entire review that EPA undertook.

If you look at the analysis of individual studies, you will find that in 17 of the 17 studies that were looked at for exposure levels, we saw a consistent effect at actual environmental levels. This is unprecedented, to find this kind of consistency.

Senator FAIRCLOTH. Is it true that a person would have to spend 800 hours in a smoke-filled work place to receive the equivalent of smoking one cigarette direct?

Ms. BROWNER. It is not appropriate to draw those kinds of linear conclusions. To just say that one cigarette is equal to 800 hours and that two cigarettes is equal to something else. This is a far more complicated epidemiological analysis that was undertaken.

Senator, I would like nothing better than to be able to simplify this for you, but this is complicated science, as well it should be. When EPA undertakes to classify something as a Group A carcinogen, that is not a light process. We spend a lot of time and a lot of energy and we undertake extensive review. We have only done it in 16 cases in this country.

Senator FAIRCLOTH. Does EPA know anything that is simplistic and straightforward?

Ms. BROWNER. Unfortunately, the issues we deal with—the protection of the public's health of our air, our land, and our water are increasingly complicated issues, but the responsibility is a significant one and one that we accept.

Senator FAIRCLOTH. How can EPA say that its review supports work place smoking restrictions when EPA only studies nonsmokers at home and completely ignores the work place exposure?

Ms. BROWNER. It is scientifically appropriate to look at the groups that you have the best control over. Those are people in their homes.

In the work environment, people move, they change jobs, they change office mates, ventilation systems vary, et cetera. You look at the data that is the best and then you make appropriate statistical extrapolations from that data, which is what we did. What we found was that people who choose not to smoke are being put at risk, and they deserve to be protected.

Senator FAIRCLOTH. But you only studied nonsmokers at home. You didn't really check people in the work place.

Ms. BROWNER. And studying the people whom we studied is appropriate.

Senator FAIRCLOTH. Do you know what the Congressional Research Service concluded about your cost/benefit assumption from banning secondhand smoke?

Ms. BROWNER. I am familiar with the CRS report. I would like to point out that it was done, as I understand it, for a slightly different purpose.

Senator FAIRCLOTH. What was their purpose as opposed to yours?

Ms. BROWNER. As I understand it, the original study was undertaken to look at the question of an excise tax as an advisable means of funding for health care.

Senator FAIRCLOTH. What was your purpose?

Ms. BROWNER. Our purpose in looking at the costs was to determine if there was a net benefit in terms of a cost/benefit analysis to society. And we did find that while there are costs associated with the construction of smoking rooms, in the words of R.J. Reynolds, they are not of such a magnitude to be unwarranted. Moreover, the benefits—the dollar amounts associated with the benefits from protecting people who choose not to smoke—exceed the cost of constructing these sorts of rooms.

Senator FAIRCLOTH. The Congressional Research Service said that your cost/benefit assumptions were totally insupportable.

Ms. BROWNER. We do not agree with that. Our study has been reviewed by others.

Senator FAIRCLOTH. Such as who?

Ms. BROWNER. I would like to point out on page 46 of the CRS report the sources that are cited by CRS, of which there are only four, and include the Tobacco Institute, say that the EPA report is scientifically deficient.

I would ask you: Is that an unbiased analysis?

Senator FAIRCLOTH. I would say that it is an unbiased analysis.

But you are going right in the face of the Congressional Research Service when they say it is insupportable.

Ms. BROWNER. We disagree with the findings of CRS. We believe that they have not looked at all the evidence, that they have chosen to look at a limited number of studies. They have looked at four studies, if you are to believe their footnotes. Hopefully, they looked at more. They only referenced four.

Senator FAIRCLOTH. But you have looked at all the evidence? That is, EPA.

Ms. BROWNER. We have undertaken a many year study.

Senator FAIRCLOTH. I am delighted to learn today, if nothing else, that the EPA is infallible.

You said in your testimony that a majority of Americans support banning smoking in public places. That was a New York Times poll that offered no alternatives.

When Gallup did a poll that offered the alternative of giving people a nonsmoking area, the results were overwhelming against a total ban and for choice.

Do you really think Americans favor total bans when they are given options and choice?

Ms. BROWNER. There have been several different public opinion polls on this issue. What EPA has recommended is that building managers and building owners, where appropriate, install separate smoking facilities so that we can protect those people who choose not to smoke. I think Dr. Elders said it well when she said that this is not really about the people who are choosing to smoke; it is about the people who are choosing not to smoke and their rights.

Senator LIEBERMAN. Thank you, Senator Faircloth.

Senator Lautenberg, I think your questions will conclude for these witnesses. They have been generous with their time and we do have two other panels we want to get to this morning.

Senator LAUTENBERG. Thank you very much, Mr. Chairman.

Ms. Browner, can you remind us of what materials there are that are classified under the Group A carcinogen list? I don't know if you have a complete list.

Ms. BROWNER. I do have a list with me. If you would like, I can read it into the record.

Senator LAUTENBERG. It doesn't need to be all of them, just name a few of those, please.

Ms. BROWNER. I will read the ones I can pronounce—arsenic, asbestos, chromium six, coke oven emissions, environmental tobacco smoke, nickel, radon——

Senator LAUTENBERG. That is good enough. I just wanted the record to reflect that we are not discussing a trivial matter here. These are poisons. That is the way to describe them.

How many reports have there been by the Surgeon General's Office on smoking and the risks of smoking, Dr. Elders?

Dr. ELDERS. I think there are more than 20, Senator. They have been going on for 30 years.

Senator LAUTENBERG. So over a 30-year period—we just celebrated the 30th anniversary of the awakening of America.

What is the largest controllable cause of death in this country?

Dr. ELDERS. I think obviously tobacco smoke is one of our largest known controllable causes of death in America.

Senator LAUTENBERG. We are sure those people are dead, right? I don't want some bureaucratic analysis here.

I don't want to trivialize it, but in one year we lose more people than we have lost in some of the major wars that we have fought. We lose far more than we do with accidents on the road. This is a threat to our society. If we establish first that smoking itself is a danger, then obviously we can make the case very comfortably, I believe, and using the best scientific methodology with people who have outstanding reputations to make the case to ward off the risks of secondary smoke.

It is pitiful that the tobacco industry persists in denying what is in front of their faces.

I have a very good friend who runs one of the major tobacco companies. He asked me what I had against the tobacco companies. I told him that I had nothing against them. My interest is in protecting the citizens.

He said, "I think you have pushed us too hard."

I told him, "I'll tell you what. You, your children, your father—you start taking up smoking and smoke two packs a day, have a certified accountant or a doctor confirm it, and then maybe we'll take a second look."

Well, there are no takers. I am sure it is not because they couldn't afford it.

I would also make mention of the fact that there was a report, as I indicated in my opening remarks, in the New York Times over the weekend that showed a company suppressing information and recognizing that they had serious hazards in their products. The question was whether or not they were going to let it all hang out or whether they were going to hide that information. They chose to hide it. There was one fellow who tried to accept the responsibility in 1963 and his testimony was suppressed.

We are going to hear later from Mr. Christopher Coggins, a researcher at R.J. Reynolds. In his written statement, he makes the following assertions. I would ask if either of you agree with them.

He states that chance could play a role in the statistical associations in the EPA report.

Ms. Browner?

Ms. BROWNER. No, we do not agree that chance—in fact, if you look at the study that we conducted and this chart that shows what the probability of occurrence by chance is—1 in 10,000, 1 in 10 million, 1 in 1 billion—that is not chance.

Senator LAUTENBERG. That is a fairly significant sampling.

He also states that a statistical phenomenon called confounding cannot be ruled out as an explanation for the statistical associations in the EPA report.

Ms. BROWNER. Again, Senator, we do not agree with that.

Senator LAUTENBERG. Dr. Elders, you said that you and five former surgeons general endorse the Smoke–Free Environment Act.

Dr. ELDERS. Yes, sir.

Senator LAUTENBERG. Where these all appointed by a Democratic Administration?

Dr. ELDERS. No, sir.

Senator LAUTENBERG. Is it the most current five?

Dr. ELDERS. It is the most current five. The last two were Republican.

Senator LAUTENBERG. And honorable and distinguished people.

Dr. ELDERS. Wonderful surgeons general.

Senator LAUTENBERG. So they have endorsed this Smoke-Free Environment Act?

Dr. ELDERS. Yes, sir.

Senator LAUTENBERG. Do you think there is any safe level of exposure to children for environmental tobacco smoke?

Dr. ELDERS. Based on the EPA study, as far as we know, there is no safe level of exposure.

Senator LAUTENBERG. As adults, we can ask people—and I don't mind doing it; I do it politely—not to smoke in the area in which we are dining or what have you. Children don't have that same kind of power or courage. Therefore, does it make the case for Government's intervention on their behalf something that we should do?

Dr. ELDERS. Senator, I feel that we must intervene on behalf of the most valuable resource we have; our children.

Senator LAUTENBERG. Amen.

Does the recent New York Times article showing the reluctance or the scheme by Brown and Williamson Tobacco Company hiding their internal studies linking smoking and lung cancer surprise you?

Dr. ELDERS. I certainly feel that there have been multiple very good studies showing an association between lung cancer and cigarette smoking. I am sure that the tobacco industry has had excellent scientists. They have done very excellent work. So the fact that they had the data—if they did the studies, I am sure they found the same as other scientists. The facts are the facts.

Senator LAUTENBERG. Both of you are parents, right?

Ms. BROWNER. Yes.

Senator LAUTENBERG. And I think eminently qualified professionals. I supported the appointment of each of you to your present distinguished office.

Do you think tobacco companies have the best interest of children in mind when they advertise as they do or when they protest our trying to protect them from secondhand smoke?

Ms. BROWNER. It seems so simple. We should protect the children of this country. I am concerned that there are people in this country who do not have our children's best interests at heart. Why would we take healthy children and expose them to something that we know is likely to cause them problems, to make them ill? Why not protect our children? It seems simple.

Senator LAUTENBERG. I saw the interviews after Congressman Waxman's hearing of some of the tobacco executives. In a couple of cases, they were asked if they would encourage their children to smoke and they were unanimous in that they absolutely would not.

Do you think tobacco companies try to lure young people to pick up smoking?

Dr. ELDERS. Senator, we know that 90 percent of the people who smoke start smoking before age 19. We know that tobacco is addictive. They must recruit 3,000 young people per day in order to maintain the present level.

Senator LAUTENBERG. Is smoking allowed in either of your departments?

Ms. BROWNER. No.

Senator LAUTENBERG. That's pretty good evidence that we ought to take from those who know best, perhaps, about the health and environment. We ought to use your example and proceed with the Pro–Feds legislation.

Thank you very much.

Mr. Chairman, thank you.

Senator LIEBERMAN. Thank you, Senator Lautenberg.

Senator Faircloth has asked the Chair if he could ask one more question. With your indulgence, I would like him to do that.

Senator FAIRCLOTH. Dr. Elders, this may not be germane, but it is close to it.

Heart disease is the number one killer in the United States, followed by all forms of cancer. Yet we are currently spending more money on AIDS research than either heart disease or cancer. Do you support shifting funds so that the Government spends the most money on the number one killer rather than on the number nine killer?

These are figures from your Department; 36.2 percent of the Federal money was spent last year on AIDS, which accounted for 1.3 percent of the deaths. Heart disease got 5.3 percent of the money and accounted for 41.8 percent of the deaths. Cancer, lumped together, got 30.3 percent and accounted for 28.2 percent of the deaths. How can we justify this massive expenditure on something that is our ninth killer. Do you think that is a good expenditure of our money?

Dr. ELDERS. Senator, we know that AIDS is a disease in our country that is destroying our bright, young people. We have not found the cure for this disease. We do not have a vaccine for this disease. The only thing we have is education and to try to treat them as best we can. I feel that if we do not find a vaccine, do not find a good drug, and we do not educate our bright, young people, Senator, we are going to lose our entire society. I feel that we must continue to invest in trying to find a way to take care of this disease in our society.

As you know, most of the people who die with heart disease and cancer are our elderly population. We all will probably die with something sooner or later. We have been investing certainly in cancer and heart disease. And I feel we should continue. I am not downplaying that. But I am saying that we are losing the people who are going to pay my Social Security and that bothers me.

Senator LIEBERMAN. In the exercise of the chairman's discretion and in the interest of balance, Senator Lautenberg has now asked for one last question.

Senator LAUTENBERG. I just want to know, Dr. Elders, are there any medications that can alleviate the symptoms of heart disease and help in direct ways to extend life for those who have had heart damage?

Dr. ELDERS. Yes, sir. I think there are multiple medications that are available. We have some that may help a little bit, but we certainly——

Senator LAUTENBERG. Do we have anything that says we are going to make your life pleasant until the day you go?

Dr. ELDERS. No, sir.

Senator LAUTENBERG. Thank you very much, Mr. Chairman.

Senator LIEBERMAN. I thank you both. It has been spirited. You have been very informative and helpful to the committee as we consider these two bills that are before us. We look forward to working with you as these bills work their way through Congress.

Thank you both very much.

I now call the second panel, Dr. Christopher Coggins, principal research and development toxicologist, R.J. Reynolds, Winston–Salem, North Carolina; and Dr. Aubrey Taylor, professor and chairman, Department of Physiology, University of Southern Alabama School of Medicine, appearing on behalf of the American Lung Association.

We welcome both of you gentlemen and thank you for being with us. We look forward to your testimony. This issue involves broad policy judgments, but a lot of it also comes down to some detailed science. We are trying to learn so that our conclusions are informed.

Dr. Coggins, we look forward to your testimony now. We are going to run the clock on you and hope that both of you can stay within the 7 minutes.

STATEMENT OF CHRISTOPHER COGGINS, PRINCIPAL RESEARCH AND DEVELOPMENT TOXICOLOGIST, R.J. REYNOLDS TOBACCO CO., WINSTON-SALEM, NC

Dr. COGGINS. Good morning, ladies and gentleman, members of the committee, Mr. Chairman.

My name is Dr. Chris Coggins. I am a principal scientist with the R.J. Reynolds Tobacco Company. I am also a board-certified toxicologist. I have performed toxicological evaluations on tobacco smoke since 1976. I appreciate this opportunity today to testify on behalf of the Tobacco Institute.

Rather than repeat the scientific criticisms of EPA's report contained in our written statement, today I shall first focus on a very basic issue: What are the amounts of environmental tobacco smoke that nonsmokers are in fact exposed to? I shall then explain some of the significant flaws in the data that the EPA report is based on. Finally, I will illustrate for the subcommittee just how fragile the EPA's conclusions are in light of data published subsequent to the release of its report.

Just what is environmental tobacco smoke? You must understand that environmental tobacco smoke is not the same as mainstream smoke or side-stream smoke. It is hundreds to thousands of times more diluted. How much environmental tobacco smoke are nonsmokers exposed to? The answer is: very little.

A review in 1993 of published data examined measurements of air quality in smoking and nonsmoking homes. The average concentrations of respirable suspended particulates were 22 micrograms per cubic meter for nonsmoking homes and 49 micrograms per cubic meter for smoking homes, giving an average difference that is presumably due to smoking of 27 micrograms per cubic meter. There were similarly small differences for smoking and nonsmoking offices, public buildings, restaurants, and transportation.

A microgram is a millionth of a gram. But this set of units may not be familiar to everyone here, so let's look at a simple analogy using everyday terminology.

If I had a large-sized, 12-ounce can of hair spray, and if I had an unlimited number of houses, each with a floor plan of 2,000 square feet and with 8-foot ceilings, amongst how many houses must I distribute the hair spray, evenly throughout, to increase the background concentration of particulates by that 27 micrograms per cubic meter. The answer is that I could spray the contents of that can of hair spray evenly throughout the air contained in every room in almost 30,000 houses.

One of the basic tenets of toxicology is that the dose makes the poison. All things are poison, depending on the dose. Concentrations of micrograms per cubic meter represent such trivial doses that it is scientifically implausible that they could result in meaningful toxicological activity.

In fact, animals exposed to environmental tobacco smoke at concentrations hundreds of times higher than those I have just described show no meaningful changes at all. I personally conducted that work.

Moving onto the EPA report, first, the EPA did not conduct any original health studies. Instead, the Agency based its so-called risk assessment on existing epidemiology studies. The EPA's analysis of those studies simply does not meet the Agency's own guidelines for risk assessment, nor does it conform to established scientific principles.

The EPA reviewed 30 world-wide epidemiology studies on spousal smoking and lung cancer. Mr. Chairman, 80 percent of those studies were not statistically significant. The 30 studies were extremely variable with relative risks ranging from a high of about

2.5 to well below 1. The EPA's meta-analysis—which is a form of averaging—of 11 U.S. studies, none of which were statistically significant, produced a relative risk of 1.19.

Regardless of your views on environmental tobacco smoke, these reported associations are weak. And the relative risks go down as more studies are added to the meta-analysis, as shown in my first exhibit.

Epidemiologists interpret weak associations cautiously largely because such associations are particularly susceptible to being produced by confounding factors. Studies published since the EPA report was released confirm both the existence of confounding and its importance when interpreting data on environmental tobacco smoke and lung cancer.

In my second exhibit, I show some risk factors for lung cancer identified in a recent study funded by the National Cancer Institute, a study that was not considered by the EPA. On the bar chart, you can see that the major factor is a diet high in saturated fat. Weaker risk factors include consumption of citrus fruit and juice and a history of previous lung disease. The overall relative risk for spousal smoking is 1.0, which means that there is no increase in risk.

These new data demonstrate that a diet high in saturated fat may play a significant role in the development of lung cancer in nonsmokers. Yet none of the studies relied upon by the EPA obtained information on dietary saturated fat, much less controlled for this important factor.

In framing public policy on this issue, this subcommittee should consider the following scientific facts:

One, the amounts of environmental tobacco smoke that nonsmokers are likely to be exposed to are vanishingly small;

Two, as such, they are unlikely to be biologically meaningful;

And three, the reported association between environmental tobacco smoke and lung cancer could easily be the result of confounding, given that it is such a weak association and given the strength of other known risk factors, such as diet.

Thus, any effort to ban smoking in all work places and public buildings is motivated not by sound, objective science, but by political considerations of what constitutes correct behavior. The Government should not make this decision for the private sector.

Thank you.

[Charts used by Dr. Coggins follow:]

Exhibit used in testimony at a Senate hearing 5/11/94

Cumulative meta-analyses, by year, of US studies.

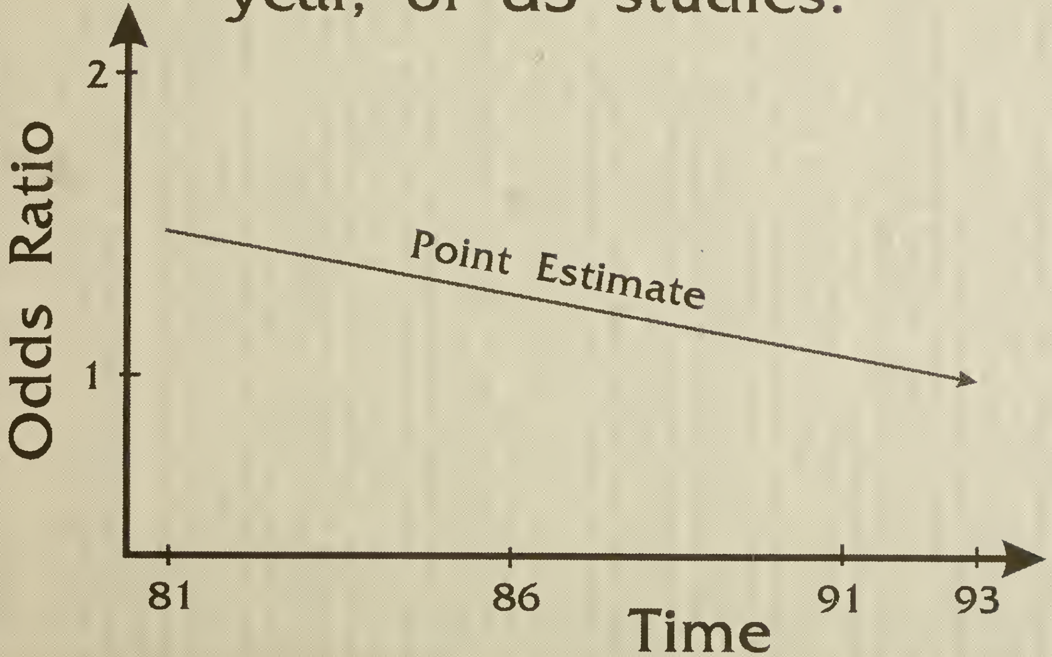
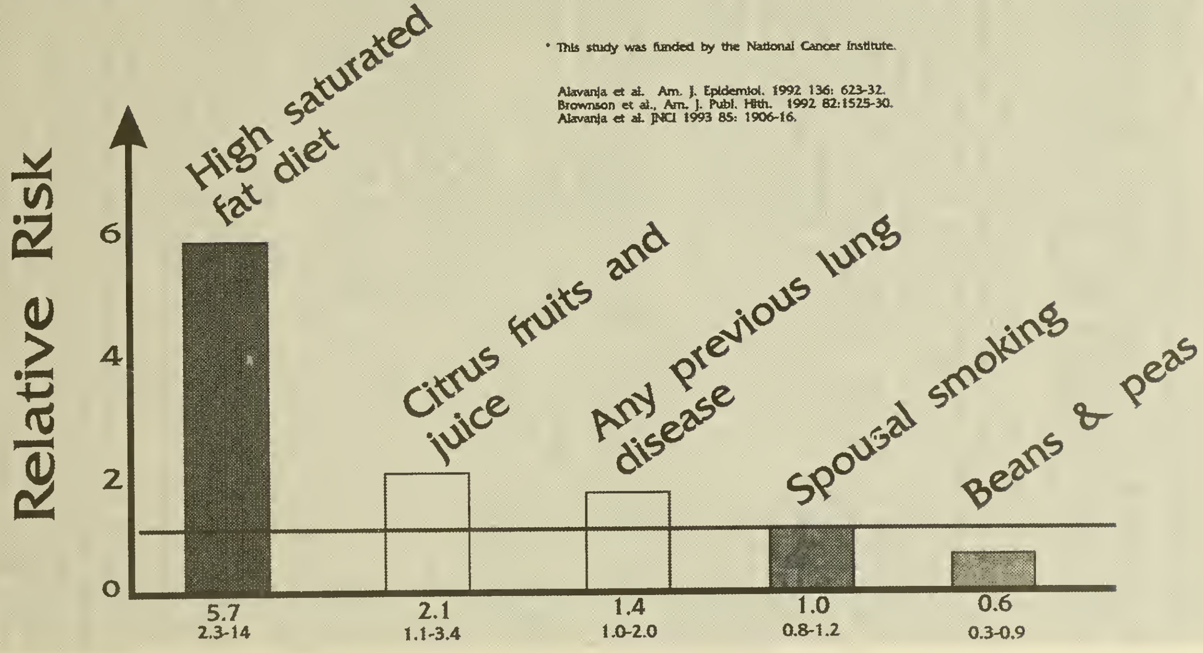


Exhibit used in testimony at a Senate hearing 5/11/94

Relative risk for lung cancer (all types) in the 432 nonsmoking women from Missouri*.



* This study was funded by the National Cancer Institute.

Alavanja et al. Am. J. Epidemiol. 1992 136: 623-32.
Brownson et al., Am. J. Publ. Hlth. 1992 82:1525-30.
Alavanja et al. JNCI 1993 85: 1906-16.

Senator LIEBERMAN. Thank you, Dr. Coggins. I look forward to the question period with you.

Dr. Taylor, welcome.

STATEMENT OF AUBREY TAYLOR, PROFESSOR AND CHAIRMAN, DEPARTMENT OF PHYSIOLOGY, UNIVERSITY OF SOUTHERN ALABAMA SCHOOL OF MEDICINE, ON BEHALF OF THE AMERICAN LUNG ASSOCIATION

Dr. TAYLOR. Mr. Chairman and members of the committee, I thank you very much for allowing me to be here today.

I am speaking on behalf of the American Lung Association and the American Cancer Society and the American Heart Association, united as the Coalition on Smoking OR Health. It is an honor and a privilege to be here. I think you are discussing what is one of the most pressing health problems in the United States, Environmental Tobacco Smoke (ETS). I commend you for doing that.

Rather than go through a lot of the things that have been discussed before me, I want to pass on those, but again I want to emphasize how many of our past surgeon generals have looked at the ETS problem and discussed it. It started out basically saying that we think ETS is a problem. Then we began to look at more data and saw more of a problem.

I might tell you that there were cancer studies on lungs done before the EPA report on ETS. There were several of them done. They predicted almost the same number of deaths due to people having lung cancer by being exposed to environmental tobacco smoke. So it is not just the EPA that reports this data, but other studies have been published on this.

I want to convey to you that we move from thinking that ETS is a problem to having several studies showing that ETS is a problem, and then the EPA analyzing all these problems. And I might add that the EPA people who did these studies are experts—I wish I knew as much about epidemiology and statistics as this group of people. These people were chosen because of their expertise in the area of epidemiology and cancer risk factors. I want that to be carefully noted by everyone.

Now I would like to talk today about something everybody mentions but doesn't really get down to the facts, and that is the effects of passive smoking on producing cardiovascular disease.

I use the term passive smoking for a reason. Doonesbury had a very interesting cartoon. I am sure many of you see Mr. Butts' cartoons. Mr. Butts was discussing passive smoking in one of these hearings. A Congressman said, "What do you think about the number of people dying from heart disease, 35,000 to 40,000 people each year, due to breathing environmental tobacco smoke—passive smoking?"

Mr. Butts said, "I don't think much about it. They bring it on themselves."

One of the Congressladies he always uses in his cartoon was sitting in the chamber—before you stopped smoking in there—she had a gas mask on. Of course, Mr. Butts was helping the ETS with his smoking. She looked up and said, "What do you mean by saying that? In other words, I am not smoking."

He said, "Yes, but you are passive."

So perhaps rather than using the term "environmental tobacco smoke", "passive smoke" is what should be said when we talk about children sitting around and having to breathe in smoke. And if you don't think smoke in the environment affects you, consider that right now every 2 minutes you are turning over the air in your lungs, whether you want to or not. That is all I will tell you. If you don't think what is in the air of our environment gets into our lungs, that is absolutely incorrect.

I would like to very quickly go over some of the first studies on active tobacco smoking. I think all of you know the American Heart Association, which is a very conservative organization. They published their first assessment of active tobacco smoking on producing cardiovascular disease in 1977. I think you know that there are over 400,000 deaths per year due to active cigarette smoking and that 200,000 of these deaths are due to cardiovascular disease.

The other thing I want you to know is that 1.5 million people have heart attacks each year, about a third of whom die. Of these, over 50 percent are male and 48 percent are female. Over 3 million in the United States have angina. Some of your senatorial friends probably have angina. You know what that is? It is commonly known as chest pain. It usually occurs upon exertion. Each year there are about 350,000 more heart patients with angina. That means that every time they exert they may have another heart attack because this pain is associated with insufficient blood flow to the heart.

The major causes of these heart attacks is the formation of atherosclerotic plaques. These plaques simply clog up a blood vessel going to the heart. It is just that simple. If that heart muscle doesn't get sufficient blood, it is going to die. If it is severe enough, whoever has the clogged up blood vessel in their heart will also die. It is that simple.

Cigarette smoke contains a lot of harmful substances. You have heard them discussed in the panel before. But I want to talk for a moment about nicotine, carbon monoxide, and environmental tobacco smoke in general since I think they can lead to strokes and heart attacks because they represent substances which can start the formation of atherosclerotic plaques.

Some of this discussion is more modern biology that we have talked about today. This is what I want to talk to you about and have this in your mind as you tackle the difficult job of assessing the health hazards of environmental tobacco smoke.

We know that nicotine causes increased heart rate and higher blood pressure in humans. Do you know what that makes your heart do? It makes your heart work harder. What if your heart is damaged a little bit? That means it can't work harder, but your body will ask your heart to work harder anyway. In turn, these conditions force the heart to work.

Tobacco smoke also activates circulating white cells. This takes a little bit of further explanation. In your body, you have a lot of cells that are constantly being bombarded with things we shouldn't be doing to these cells. But they become activated. These cells are called neutrophils. When they are activated, they release a substance called an oxidant. I think you all know what an oxidant is.

You have seen rust and you know how a little piece of rust will start forming and finally rust the whole nail.

This is exactly what happens to the lining of blood vessels. It is sometimes a long process, and other times not so long a process. As these white cells release this damaging compound, endothelial cells maybe only slightly damaged. But if you continue this process, then perhaps there is enough damage to the endothelial barrier for platelets to adhere.

Platelets are in our blood for a very important reason—clotting. That is why you don't bleed to death every time you nick yourself shaving. It is important to have them. But the major thing that they are not supposed to do is stop up blood vessels unless necessary. There is evidence now in the literature on the effects of passive smoke—and on the impact of high ETS levels. We can argue all these experimental conditions, but the data clearly shows that passive smoking can activate these neutrophils. That is a fact. We are going to have to extrapolate what it might mean.

Finally, I would like to discuss carbon monoxide with you because carbon monoxide decreases the amount of oxygen the blood can carry. Now, if you need more oxygen to your heart because of a plaque formation or because of a partially occluded blood vessel, you are going to have a problem getting efficient blood flow. If you have angina and you happen to walk into a room full of smoke—I wouldn't be surprised if someone shouldn't try to study this effect. You sometimes are going to have angina.

I want to very quickly go through the studies and I don't wish to delay you any longer than I have to because I could talk about this all day.

I am not an epidemiologist. I have no weight at all, in this issue except what I would like to see is to stop people from smoking where I am. That is all I want.

I published a paper in *Circulation*, along with Drs. Kazema and Johnson of Harvard Medical School, which I will leave with you. It is published in *Circulation* in the American Heart Association Journal on environmental tobacco smoke and cardiovascular disease.

Before that, a paper was published that evaluated 10 published epidemiological studies. All except one had a risk factor greater than 1. I don't want to go into the science of risk factors with you, but that means that all studies except one had a positive correlation of heart disease associated with ETS, with the overall risk factor being 1.3.

This study was done by Glatz, who predicted that 37,000 cardiovascular deaths occurred every year due to passive cigarette smoking.

The study I really think was superb was published in JAMA by the American Medical Association. I also want to leave that study with you, so that some of your people can look at it and make up their own minds as to what is being said in this paper. Dr. Steenland evaluated nine epidemiological studies with risk factors varying from 0.9 to 3.0. That is what the tobacco people are telling you when they say that sometimes a study has a risk factor of less than 1.

Assuming the observed cardiovascular risk factors due to environmental tobacco smoke exposure, Steenland predicted that 35,000 to 45,000 ischemic heart disease deaths occurred each year due to ETS.

He used another study by Hesling. Because one of the arguments presented about epidemiological studies is: how do you know people didn't used to be smokers? He studied the data to evaluate what happened in nonsmokers as well as former smokers. That data is also considered for you.

This study was done in the United States. It was the largest study that had people who did not smoke living with a smoker.

I also want to say that in five of the studies that Steenland analyzed for the overall risk factors, five were cohort, three controlled for cardiovascular risk factors—cholesterol, high blood pressure, and obesity—and what he produced was a very academic piece of work. I want you all to look at it and let your people look at it. It is not difficult to follow, and is an excellent epidemiological study.

I want to summarize my presentation——

Senator LIEBERMAN. Doctor, I apologize for interrupting, but we are over the time allowed. If you could just close briefly, we will put the rest of your statement in the record.

Dr. TAYLOR. I am sorry to go over, but I got carried away.

In our paper, published in *Circulation*, we also predicted 35,000 to 40,000 deaths by evaluating all of these published findings on ETS and heart disease.

Our final recommendation was to ban smoking in public places. I did not highlight this in the paper, but you may see it there in the last paragraph. We also recommended that we needed to enhance public awareness of the dangers of environmental tobacco smoke by educational means.

I have heard about education today from the Surgeon General, and that is extremely important because children are exposed to parents who smoke every day. They have no protection from ETS.

In Mobile, Alabama I went to several elementary schools and talked to many children who live all over the city of Mobile. I went to some 25 elementary schools and it was a great awakening. I would urge everybody in the audience and everybody here who cares about the health of these children to go out and talk to them about environmental tobacco smoke and the health problems it produces.

I thank you for giving me this time, and the Coalition on Smoking OR Health supports the ban on smoking in public places.

Senator LIEBERMAN. Thank you, Dr. Taylor.

You have just responded to the question I was going to ask first, which was about whether you support the proposal to ban smoking in public places. You answered affirmatively.

Dr. Coggins, I presume you would oppose that, based on the testimony you have given.

Dr. COGGINS. I think that a ban is a policy, but if that policy wants to be based on science—and I think it should be—then I think the science is lacking. I don't think scientists should make policy. That is your job; but if you want to have your policy supported by science, my message to you is that a lot of that science is very weak.

Senator LIEBERMAN. Based on your conclusions about the science, is there anything you would recommend that we policymakers and lawmakers do regarding the regulation of secondhand smoke?

Dr. COGGINS. I think one of the messages I had in my text is the real basis for everything, and that is that the dose makes the poison. We are talking about such vanishingly small concentrations of smoke—micrograms per cubic meter. I know my analogy may not appeal to everyone, but it is the best one I can come up with that puts into place volume and mass. That can of hair spray over 30,000 houses is just such an infinitesimal dose, how can you really expect any biological activity.

Then I put into context that once you have made the hypothesis, the way scientists then follow on is to do studies that will examine the hypothesis. That is what we did at R.J. Reynolds. We performed some animal studies. We exposed some animals. This is a very easy way of finding out what is going on because you can control for things like confounders. In an animal study you don't have to worry about the high-fat diets, radon, or anything else.

So we performed a study where we exposed animals to what we thought was at the time a real world concentration of environmental tobacco smoke. Then we said that we would multiply that by 10 for a safety factor. Then to prove that our tests would work, we multiplied that by 10. So we had real world times 10 and real world times 100. The overall factor was about a 400-fold exaggeration.

We found absolutely nothing in those animals exposed to 400 times the 27 micrograms per cubic meter.

Senator LIEBERMAN. Do you contend with the conclusion that was presented by the first panel that the chemical components of so-called mainstream smoke inhaled by smokers are the same as the chemical components of secondhand smoke? But you say the question is just how much of a dose?

Dr. COGGINS. Exactly.

Senator LIEBERMAN. But would you agree that they are chemically similar?

Dr. COGGINS. I think so. I think they are chemically similar, but they are quite different to the extent that environmental tobacco smoke is so massively diluted and aged in the process of the formation of environmental tobacco smoke. It goes through aging and it goes through a massive amount of dilution. There are a few changes that go on during that aging and dilution, but the end product is a smoke with perhaps 50 known components.

Senator LIEBERMAN. Dr. Coggins, let me ask you about your second chart, which deals with the so-called confounders. But basically, there are other factors that might be at work that might have contributed to the incidents of cancer in the various studies.

Am I understanding it in lay language?

Dr. COGGINS. You have got it.

Senator LIEBERMAN. For instance, a diet high in saturated fats might have been at work in the studies that the EPA used as the basis for their report, although EPA did not consider that.

Dr. COGGINS. That's correct.

Senator LIEBERMAN. I did not read the studies themselves but I read a good part of the EPA report. I noted that they not only used studies from the United States, but they did take studies from other countries. They used studies from China and Japan, as I recall. Here I am going on my common understanding of the fact that the Japanese and Chinese generally have a low-fat diet whereas we in the United States have a high-fat diet.

Does that affect the questions that you have raised as to the conclusions, or does it strengthen, in your mind, the EPA report's conclusions?

Dr. COGGINS. First of all, you got it right. A confounder is a factor other than the one under study that affects the disease under study. So it comes from the Latin word "to mix".

On the chart—this is the Brownson Study. They have shown that the diet high in saturated fats has a relative risk of almost six, whereas spousal smoking is 1.0. So from the Brownson Study, by far the most significant risk factor for lung cancer is a high-fat diet.

In relation to your question on diet in the non-United States studies, there is very little information gained from most of those studies on other confounders. They corrected for the basic ones like age and sex and perhaps a couple of others. But as far as I know, none of the 30 studies actually obtained data on diet, and therefore they could not correct for that factor.

Senator LIEBERMAN. I appreciate your answer.

Hearing your criticism of the EPA study, my question is whether it might be described as inadvertent. Did they inadvertently consider the so-called confounders by taking some of the studies from countries which have a low-fat diet where presumably the people studied also had a low-fat diet?

Dr. COGGINS. Science is one of those odd things. This report is very new. There was no statement available when it was written on the role of saturated fat. But at the same time, there have been indications in animal studies that perhaps a high-fat diet could be linked to lung cancer.

So my criticism of the EPA report is really their statement that they examined for potential confounders, couldn't find any, and went on regardless. I am saying that here is at least one that could have had a major effect. In fact, in the Brownson Study it did indeed have a very major effect on those 432 nonsmoking women.

Senator LIEBERMAN. Dr. Taylor, you have testified today regarding the cardiovascular effects of secondhand or passive smoke. You have estimated in your testimony that between 35,000 and 40,000 cardiovascular deaths each year are attributable to secondhand smoke.

As you probably heard, there is a CRS memorandum coauthored by Dr. Gravelle, who will testify in the third panel, that criticized the American Medical Association estimate that stated that passive smoking may kill as many as 53,000 Americans annually. That estimate attributed a little more than 37,000 of those deaths to heart disease.

The CRS memo states that a more accurate estimate of smoke-related deaths in nonsmokers based on a physical extrapolation method would be 1,000 deaths with 700 resulting from heart disease.

I don't know whether you are familiar with the study. If so, what is your opinion?

Dr. TAYLOR. That is just absolutely wrong. But let's do something very simple in this. Let's not get very technical.

I accept that 3,000 lung cancer deaths occurred due to environmental tobacco smoke. I think the EPA Study is one of the most magnificent and scholarly pieces of work we have had in this country in many years in science. I will say that unequivocally and I don't think you will have many scientists say otherwise.

But the problem is that the studies I quoted tried to correct the other risk factors. She didn't quote our study, which looked at all the studies and tried to come up with a conclusion, or the one by Steenland. I wanted that to be included in here because some studies did look at cardiovascular risk factors as well as could be done. She was saying that all these other factors do confound it. In fact, I think that is one of the things we have to consider when we think about the health hazards of environmental tobacco smoke. It is not just environmental tobacco smoke you are preventing out there, but you are preventing environmental tobacco smoke from adding on top of another risk factor.

Senator LIEBERMAN. Thank you, Dr. Taylor.

My time is up.

Senator Faircloth?

Senator FAIRCLOTH. Before I begin, I would like to ask you to keep the record open for a week, if you would, so that we could add some things to it.

Senator LIEBERMAN. We certainly will. We will do it for even more than that; we will keep it open for 2 weeks.

Senator FAIRCLOTH. Dr. Coggins, are you a native of eastern North Carolina?

Dr. COGGINS. No, sir.

[Laughter.]

Senator FAIRCLOTH. What is the relative risk of the EPA's conclusions about environmental tobacco smoke compared with your driving to the hearing today?

Dr. COGGINS. I was driven, so I don't know.

[Laughter.]

Dr. COGGINS. But I do know that the chairman of the Science Advisory Board, when asked that question at one of the press conferences, said that the relative risk of lung cancer from exposure to environmental tobacco smoke was probably less than what you took to get here through Washington, DC traffic.

[Laughter.]

Senator FAIRCLOTH. How does living with a person who smokes compare with smoking yourself? What is the ratio?

Dr. COGGINS. First of all, I agree with one of the comments made in the earlier panel, that it is very difficult to make a direct extrapolation from environmental tobacco smoke to a cigarette equivalent. There are lots of problems.

But since you asked the question, I can take you through a calculation that was recently published and I can give you the report.

This is a gentleman who published the figure of 27 micrograms per cubic meter for the home. He also measured the concentrations in offices where smoking is allowed and restaurants. He made the calculation for what is the maximally environmental tobacco smoke-exposed person. This is someone who is exposed at home, is exposed to smoke in transportation on the way to work, is exposed to smoke at work, works in the evening in a bar—this is someone who is maximally exposed.

This researcher then calculated the amounts of time this person would spend in those variety of places and then figure out just how much smoke that person would gain in a day. It was about 60 to 70 micrograms of respirable suspended particulates, which he then went on to calculate—admitting that there are some problems with his extrapolation. But that would be equivalent to perhaps one to four cigarettes a year.

Senator FAIRCLOTH. How many?

Dr. COGGINS. That would be one to four cigarette-equivalents a year for the maximally environmental tobacco smoke-exposed person.

Senator FAIRCLOTH. In other words, if you are living with somebody that smokes, your inhalation of smoke would be comparable to about one to four cigarettes a year.

Dr. COGGINS. That is the figure that is quoted by Dr. Holcolm in his paper, yes.

Senator FAIRCLOTH. Don't worry about extrapolations. The EPA uses them all the time to prove anything they want.

How exactly can the EPA review 11 independent studies and conclude something collectively from the 11 that none of the 11 individual studies indicated individually?

Dr. COGGINS. The EPA used a technique called meta-analysis. Meta-analysis is the combination of 11 studies into one. Meta-analysis is used in medical circles, for example for comparing various clinical trials of the same drug. You are allowed to do meta-analysis when the basic designs of the experiments are the same. I believe that the designs of these 11 studies were very, very different and that they should never have been combined into a meta-analysis.

I am not sure how the results come out as significant as they claim to be. They are very, very borderline, but the figure of 1.19 comes out as the point estimate using these non-standard 90 percent confidence limits. The lower confidence limit has to be above one to become statistically significant—and I don't want to talk too much about statistics today—but the lower value from the EPA, admittedly using these funny standards, was 1.04. It is as close as non-significance as it possibly can be.

I heard Professor Alvin Feinstein from Yale University when he saw these figures at a hearing last year saying that he congratulated the tailor who designed that value.

Senator FAIRCLOTH. What did he say?

Dr. COGGINS. He said, "I congratulate the tailor who manufactured that value."

Senator FAIRCLOTH. Tell me what it means in good science when you change the confidence level, as the EPA did. The answer from

Ms. Browner became so convoluted so that I lost where I was going. Tell me what that means, if you can, in good plain English.

Dr. COGGINS. It is very easy, and it is also easy to understand and difficult to explain.

When you move from a 95 percent confidence limit—in the 95 percent confidence limit, you accept a 1 in 20 chance of being wrong in placing that point estimate somewhere in the bounds you have established. That is what scientists throughout the world use.

When you use a 90 percent confidence limit, you accept a 1 in 10 chance of being wrong. You have doubled the chance of being wrong. It also makes it a lot easier to achieve statistical significance because the 90 percent bands are narrower than the 95 percent bands, so it is easier to exceed the threshold value of 1.00.

So they obtained a more significant value and they doubled the chance of an error.

Senator FAIRCLOTH. So if you wanted to make the possibility of being damaged by passive cigarette smoke look greater, you would lower the confidence level?

Dr. COGGINS. I think that is correct. I wasn't quite sure the way you put it. But I think a simpler way to say it is that you have doubled the possibility of an error.

Senator FAIRCLOTH. What is a Group A carcinogen?

Dr. COGGINS. A variety of different——

Senator FAIRCLOTH. Are there any in this room?

Dr. COGGINS. I am sure I can find lots of them. I am sure there are lots in here. We heard a lot about arsenic, cadmium, and there are permissible amounts of Group A carcinogens in this glass of water. I am allowed probably 60 nanograms of arsenic per liter in this glass of water.

Does that answer your question?

Senator FAIRCLOTH. It does, but I am afraid to drink any more water.

[Laughter.]

Senator FAIRCLOTH. My time is about up, so I am going to ask this in the form of a question.

In the time I have left, could you condense and comment on Dr. Taylor's opening statement?

Dr. COGGINS. Dr. Taylor's statement is on the epidemiology of cardiovascular disease, which was specifically not included in the EPA Report, as you know. It is based on the papers he mentioned, which refer back to another paper. I think the original paper was in 1987 by Wells.

Basically, the attributable death numbers—the way they are calculated is a statistical procedure, just the same procedure as the 434,000 we were talking about. You take the relative risk or odds ratio and you plug that into a statistical formula, called the attributable risk. This formula assumes that none of the other factors are involved. You multiply that attributable risk by the population at risk—garbage in, garbage out, in my opinion—and you get this figure of 55,000 out.

I don't think it is a meaningful figure and I don't think the 434,000 is a meaningful figure for the same reason. It is a manufactured statistic.

Finally, the relative risk that Dr. Taylor mentioned for environmental tobacco smoke and cardiovascular disease was 1.3. The Surgeon General has pointed out that the relative risk for mainstream smoking is 1.7. Several of the studies that Dr. Taylor mentioned in his meta-analysis that was used to arrive at the 1.3 had values higher than 1.7. In other words, you had a higher risk for passive smoke than you had for mainstream smoke. I think that is biologically implausible.

Senator FAIRCLOTH. Thank you.

Dr. TAYLOR. Do I get to speak to this question at all?

Senator LIEBERMAN. Sure.

Dr. TAYLOR. The reason I wanted to say something about that is that Douglas Dockery, from the Coalition on Smoking, spoke to many of these problems. I will include his testimony in my package for you on these very problems I am bringing up.

Some of the things he said about including risk factors in cardiovascular disease is what we had to do. The problem there has been addressed. In one of the articles I have given you, you can see him address this.

One of the reasons is that if you use a different normal system for nonsmokers—you are saying that you are comparing nonsmokers who live with people who smoke to nonsmokers—you will find out that nonsmokers sometimes are around environmental tobacco smoke. So you cannot have the right level. In fact, they went so far in this analysis to try to look at an analysis that only looked at exposure in the home.

What I think both of these studies show—the EPA Study on lung cancer and the heart one—is that environmental tobacco smoke is a very bad health hazard and causes the death of 35,000 to 40,000 people a year.

Senator LIEBERMAN. Thank you, Dr. Taylor.

Senator Lautenberg?

Senator LAUTENBERG. Thank you very much, Mr. Chairman.

Dr. Coggins, are you a physician?

Dr. COGGINS. No, sir.

Senator LAUTENBERG. Do you have children?

Dr. COGGINS. No, sir.

Senator LAUTENBERG. A wife?

Dr. COGGINS. Yes.

Senator LAUTENBERG. Does she smoke?

Dr. COGGINS. No.

Senator LAUTENBERG. Do you?

Dr. COGGINS. No.

Senator LAUTENBERG. Why?

Dr. COGGINS. I just never got around to it.

Senator LAUTENBERG. You work for a tobacco company. You get these things cheap.

Dr. COGGINS. Actually, we don't get them cheap.

Senator LAUTENBERG. I know they do give them cheaper to employees.

Dr. COGGINS. I think some companies do.

Senator LAUTENBERG. Do you earn a salary from this company?

Dr. COGGINS. Yes.

Senator LAUTENBERG. A good salary?

Dr. COGGINS. It could be better, but it could be an awful lot worse.

[Laughter.]

Senator LAUTENBERG. Would you say that since you work for the company and depend upon them for salary—and they watch your testimony—that you have to be careful what you say, or are you are a free agent?

Dr. COGGINS. I think I have to be very careful what I say, but more importantly I have to be very careful what I say for my own scientific reputation.

Senator LAUTENBERG. I agree with that.

Did R.J. Reynolds ever do any internal studies on health and tobacco?

Dr. COGGINS. I am not quite sure what you mean by health and tobacco, sir.

Senator LAUTENBERG. You are not sure?

Dr. COGGINS. What do you mean by "studies"?

Senator LAUTENBERG. Has R.J. Reynolds ever studied the fact that tobacco may have some influence on health?

Dr. COGGINS. I don't think we have ever done any epidemiology studies like the ones we've been talking about. But the main studies we have been doing have been these animal studies that I have been talking about.

Senator LAUTENBERG. What caused them to decide to sponsor the design of a smoking room, if they hadn't done any studies? Are they just taking this stuff that is out there and saying that they had better run for cover because everybody is saying that you're not delivering a good product?

Dr. COGGINS. We have a group of industrial hygienists that are concerned with indoor air quality. We see the message that people are wanting to ban smoking with out-and-out bans. We think that there is a good half-way house with building smoking lounges or building rooms that can accommodate smokers and nonsmokers alike. If that can't be achieved, then we think we can build and design correctly——

Senator LAUTENBERG. Would you, under oath, say that R.J. Reynolds has not done—and you are not under oath, but we can swear you if you would like—has not done any studies that relate health and tobacco use?

Dr. COGGINS. I don't think I can make that statement. I have been with the company for 9 years. I don't know what they did before then.

Senator LAUTENBERG. And you are one of the senior scientists?

Dr. COGGINS. I am one of the senior scientists. That is correct.

Senator LAUTENBERG. Do you think that if we issued a subpoena we might be able to get some information about studies that have been done?

Dr. COGGINS. I don't know what happened——

Senator LAUTENBERG. Within the last 9 years, is there an insinuation that there has not been a health study performed other than the animal study? Animals count.

Dr. COGGINS. We have done a large number of animal studies over the last 9 years since I have joined the company.

Senator LAUTENBERG. Could you provide us with those documents?

Dr. COGGINS. Absolutely. It has all been published.

Senator LAUTENBERG. And with all internal documents?

Dr. COGGINS. Internal documents may be more difficult in that they probably have information on it that is——

Senator LAUTENBERG. That they would like not to have out?

Dr. COGGINS. No, that is intellectual property that our competitors would like to have. But I can certainly give you all of our publications.

Senator LAUTENBERG. Do you believe that the Brownson Study has some credibility?

Dr. COGGINS. I believe the Brownson Study has a great deal of credibility.

Senator LAUTENBERG. Do you know that Brownson said, "Ours and recent studies suggest that a small but consistent increase risk of lung cancer from passive smoking. Comprehensive actions to limit smoking in public places and work places are well advised"?

Dr. COGGINS. This is a statement made in the abstract of the article. If you were to read the data—and it is rather large and cumbersome—but when you go through the data, you will find that figure there. That is the Brownson Study. But the actual value for the overall.

Senator LAUTENBERG. He says, "Comprehensive actions to limit smoking in public places and work places are well advised."

Dr. COGGINS. I think that is a policy.

Senator LAUTENBERG. I would ask you, do you know any of the names on the list of science advisers who prepared the report for EPA?

Dr. COGGINS. Yes, I know some of the names.

Senator LAUTENBERG. Do you think these are credible people?

Dr. COGGINS. I think in general they are very good scientists.

Senator LAUTENBERG. I used to be in the computer business before I came here. You used the term of garbage in, garbage out. Are these folks garbage collectors?

Dr. COGGINS. I think in general they have very good scientific reputations.

Senator LAUTENBERG. So then how is it that there is no credibility in the work they have done?

Dr. COGGINS. I think the statement that Dr. Stolwick made at the toxicology forum meeting last year underlines a great deal of the problems with this Science Advisory Board.

Senator LAUTENBERG. But he signed onto this study, so we can't disqualify him. He signed onto the study. He gave his professional and intellectual endorsement to this. He may have said other things, but the fact is that he signed onto this study, which has subsequently been endorsed by the chairman of the National Institute of Health.

Do you know Dr. Samuel Broder of the National Cancer Institute?

Dr. COGGINS. No.

Senator LAUTENBERG. Do you buy the fact that there is any ill health effects from tobacco at all?

Dr. COGGINS. I think that mainstream cigarette smoking has been linked epidemiologically with a number of diseases. It is a risk that people take.

Senator LAUTENBERG. It is a risk that people take?

Dr. COGGINS. Yes, sir.

Senator LAUTENBERG. Does it increase their risk for significantly damaging diseases?

I heard what you said about the fats and I agree with you. But does tobacco smoking—cigarette smoking—increase the risks for the users in terms of their health and well-being?

Dr. COGGINS. Yes. I think if you look at the warnings on the pack, people are very aware of that, but there are a number of studies that say that cigarette smoking is a risk factor for a number of diseases.

Senator LAUTENBERG. Do you see that statement we have put up there? Americans think that when tobacco companies talk about health risks associated with smoking cigarettes, they say that 83 percent lie or hide part of the truth.

What do you think about that?

Dr. COGGINS. I haven't seen the results of the poll. I don't know how the question was phrased. I am not a pollster. But it would appear that we don't have the best reputation in the world. I would be the first to agree with you.

Senator LAUTENBERG. That is an understatement.

[Laughter.]

Senator LAUTENBERG. Dr. Taylor, can you explain for me what it is that has this distinguished gentleman—this scientist—so much at odds with the preponderance of views of so many others? Is there a reason? Can you think of any reason? Is everybody else doing garbage in, garbage out?

Dr. TAYLOR. No, not by a long shot. I have said several times that I think the EPA is one of the most scholarly pieces of scientific work I have seen. I know many of these individuals. I have talked to many of these individuals. They are the first to criticize the kind of work they do themselves.

If you look at any of these articles I give you, you will see that they criticize themselves very harshly and they explain the problems with doing meta-analysis. But after all, it is the best we have to work with today.

I would like the tobacco industry to come up with something better because I am sure that epidemiologists—epidemiologists are some of the hardest-nosed people I know. I have sat on several review committees for grants. I am going to tell you that if you want to do an epidemiological study, you had better have it all straight because no one is going to give you any money to do it. I can say that unequivocally.

They are excellent scientists, epidemiologists, but they have certain rules that they go by and they demand that they adhere to those rules. I am impressed with them. I am not an epidemiologist, but I am thoroughly impressed with the way these scientists work. And it is across the board. I hear it time after time.

I just think the tobacco supporters are not looking at the science. My goodness, when you can say that there are 50,000 people a year being killed by something—the data is strong on this. No one has shown me anything that says that the data is not strong on this. The tobacco industry have been saying that this is this, and that is that, but I haven't really seen anyone that has convinced me with data. And I would be the first to change. I am a scientist.

I think many times people are not fair to science. They think we have an absolute answer to everything we have. That is the reason you have risk factors and you don't have an absolute answer.

I had something I wanted to read to you because it is a statement by a very famous statistician. I know you have all been listening to all these percentiles and trying to figure what they mean. He said, "Science does not begin with a tidy question, nor does it end with a tidy answer."

I think that is the essence of science. Hopefully, you just keep going. You take data you have and do the best with it. The EPA has done an elegant study. I firmly believe that. And most scientists do.

Senator LAUTENBERG. Mr. Chairman, I thank you very much.

I just note for the record that there have been some 60,000 studies on tobacco and health and more than 20 reports by the Surgeon General's Office. I think it is fair to say that one can always challenge the evidence, but when it is so preponderant and so weighted by so many good, credible people, it is awful hard to simply challenge it, even if they are not done epidemiologically.

Senator LIEBERMAN. Thank you, Senator Lautenberg.

I actually have more questions, but I am going to submit them to you in writing and hope that my colleagues will do the same so that we can move on to the third panel that has been waiting quite awhile.

I want to thank you, Dr. Taylor and Dr. Coggins, for being here and for your testimony.

Senator FAIRCLOTH. I have just one quick question.

Dr. Taylor, I would like a yes or no answer.

Dr. TAYLOR. Okay.

Senator FAIRCLOTH. Is sun tanning dangerous to your health?

Dr. TAYLOR. Sun tanning can cause skin cancer. It certainly can. But everybody I think is quite aware of that. But see, I don't have to go into the sun unless I want to. I have that prerogative. I have the prerogative also to put on some suntan protection agent. But I don't have any prerogative when I go to take my grandson—I will tell you why I really got into this.

I have a grandson who has asthma.

Senator FAIRCLOTH. I am sorry.

Dr. TAYLOR. No, I want to get this out.

[Laughter.]

Dr. TAYLOR. I have a grandson who has asthma. We go into a restaurant and if someone is smoking back in the smoking section—which is in all the restaurants—he will immediately start wheezing. This is my grandson. I have seen a lot of people wheeze and get sick, but it scares the hell out of me when my grandson gets sick.

Senator LIEBERMAN. You have made your point. Thank you.

I thank you both.

Our third panel is Dr. Jane Gravelle, senior specialist in economic policy, Congressional Research Service, Washington, DC; accompanied by Dr. Dennis Zimmerman, specialist in public finance; and Dr. William Blot of the National Cancer Institute, a consultant to EPA and its Science Advisory Board from Bethesda, MD.

Folks, thanks for your patience. Some of you have been referred to earlier on, so we look forward to hearing from you at this point.

Dr. Gravelle, you are first.

STATEMENT OF JANE GRAVELLE, SENIOR SPECIALIST IN ECONOMIC POLICY, CONGRESSIONAL RESEARCH SERVICE, ACCOMPANIED BY DENNIS ZIMMERMAN, SPECIALIST, PUBLIC FINANCE, CONGRESSIONAL RESEARCH SERVICE

Dr. GRAVELLE. Mr. Chairman and members of the committee, my colleague Dennis Zimmerman and I would like to thank you for the invitation to discuss the statistical basis for estimates of the health effects of passive smoking.

I would like to begin by noting that we are economists and our area of expertise relates to economic analysis and the associated areas of statistical inference and quantification of effects for purposes of cost/benefit analysis and related economic policies. Our involvement in this issue was a result of a research paper on the proposed cigarette tax.

In order to assess economic efficiency issues, it was necessary to examine any costs that smokers might impose on nonsmokers. This led us to review the methodology used to assess the scientific evidence on passive smoking.

We realize that this passive smoking issue is a controversial issue. Let us begin by emphasizing what we are not saying. We are not saying that the EPA's analysis was done incorrectly, that the studies they analyzed were done incorrectly, and we are not reaching conclusions about the biological and medical issues which are outside our area of expertise, and we do not intend any numbers we have calculated to represent a risk assessment.

Our evaluation of the statistical evidence on passive smoking led to two conclusions. First, the evidence that passive smoking causes disease is far less certain than the effects for active smoking. Second, the health costs of these potential passive smoking effects, which we translated into a tax per pack, are likely to be small, although there is likely to be some uncertainty attached to these estimates.

The reasons for that view are outlined in our written testimony which we would like to submit for the record and I would like to highlight the major points made in that testimony.

Senator LIEBERMAN. Without objection, your prepared statement will appear in the record.

Dr. GRAVELLE. The evidence of a health effect from active smoking with no threshold observed for health damage is not sufficient to demonstrate a passive smoking effect since a threshold effect could occur between the lightest active smoking level studied and a smaller level of passive smoking exposure. Since theory is not certain, one approach to studying passive smoking effects is to examine epidemiological or statistical studies.

Given the small risks that are often found for passive smoking, the statistical problems are of greater concern for passive smoking than for active smoking studies. That is, when the effects are small it is more likely that some error in design or specification could be responsible for the results. Given this greater uncertainty, consistency of the results with alternative evidence becomes more critical.

In the case of lung cancer, most recently summarized by the EPA, 30 studies which examined the incidence of lung cancer among nonsmoking wives, depending on whether or not their husbands smoked, were combined into an aggregate study. The following are some of the issues discussed in our written statement that might bring some uncertainty to bear on these statistical studies.

Let me say that these tend to extend to things other than lung cancer such as children's respiratory diseases, heart disease, and other diseases that have been studied.

First, some method of aggregating these studies is necessary, but there are certain subjective aspects to performing such a combined analysis.

Second, some uncertainty attaches to the estimates in most of the individual studies, due to the need to rely on interview data to measure exposure.

Third, there is a possibility that results reflect the effect of active smoking due to the possible misclassification of former or current smokers as never smoking.

Fourth, the failure to account for other lifestyle factors that might be correlated with marriage to a smoker and that might be independently associated with lung cancer, leading to possible spurious correlation exists.

And fifth, two large new studies which were not included in the EPA Study do not seem to us to add certainty to the statistical evidence. Indeed, the results of the larger study finds no overall risk from passive smoking.

A possible alternative approach to examining the passive smoking effects would be an extrapolation from the levels of active smoking. It is discussed because it provides an alternative measure that might or might not corroborate the direct statistical evidence. The average exposure to passive smoking, as indicated in the EPA Study based on cotarnine in the urine, is about 0.5 percent or the equivalent of 0.1 cigarette per day. A linear extrapolation produces an estimate of 600 never-smoker deaths compared to the 2,000 never-smoker deaths estimated by the EPA based on statistical studies. A non-linear extrapolation yields virtually no deaths.

These discrepancies between the two approaches are even more pronounced for heart disease where linear extrapolation yields about 1,000 deaths and the statistical studies show in excess of 30,000 deaths.

These results—I will leave to you to judge what you think about these—but we see them as subject to question since the statistical estimates for passive smoking heart disease represent 26 percent of active smoking attributable deaths, despite the much lower level of physical exposure. So it is much, much larger than the estimated lung cancer deaths.

The EPA rejected this extrapolation approach for several reasons, and I can elaborate on these later if you would like, although they did review the literature and they actually used the approach themselves within passive smoking extrapolating from female never-smoker deaths that could be estimated directly from their statistical results to workplace and other exposures.

I would like to close by reminding you of the fact that both of these methodologies—direct statistical evidence and physical extrapolation—have inherent problems. But currently they are the only recourse we have in providing you with information on the issues before you. We would be happy to elaborate further on any of these issues.

Thank you.

Senator LIEBERMAN. Thank you, Dr. Gravelle. Thank you for your testimony and indicating the context in which you entered this discussion.

Dr. Blot, welcome. We look forward to your testimony now.

STATEMENT OF WILLIAM BLOT, CHIEF, BIOSTATISTICS BRANCH, NATIONAL CANCER INSTITUTE, CONSULTANT, EPA SCIENCE ADVISORY BOARD, BETHESDA, MD

Dr. BLOT. Good morning, Mr. Chairman and members of the subcommittee.

My name is William Blot. I am chief of the Biostatistics Branch at the National Cancer Institute. I have been on the staff of NCI for about 20 years conducting epidemiological research on the environmental and host determinates of cancer. Many of these research studies have evaluated the role of tobacco in cancer risk.

I am pleased and honored to be here today to discuss the conclusions of the EPA Science Advisory Board in its review of the EPA draft report on the health effects of passive smoking.

In 1990, I was asked to serve as one of about nine consultants to a standing Science Advisory Board at EPA and was requested to address several issues in a draft report on passive smoking. Perhaps the most important issue was whether the evidence was sufficient to conclude that environmental tobacco smoke is causally related to lung cancer. The Science Advisory Board met in December of 1990 and again in the summer of 1992 to discuss the EPA report and to review testimony on the health effects of environmental tobacco smoke exposure. I helped the Board prepare its recommendations, which were delivered to the EPA in the fall of 1992, and then the EPA in January of 1993 released its final report.

The Science Advisory Board unanimously concluded, based on the totality of evidence available, that the EPA was justified in categorizing environmental tobacco smoke as a Group A carcinogen, that is, as a substance which can cause cancer in people. The Board also concurred with EPA's assessment that the severity of asthma and the risk of other respiratory diseases in children could be increased from exposure to environmental tobacco smoke, but I will restrict my remarks to its association with cancer.

Over 30 epidemiological studies conducted in the United States and abroad have evaluated the risk of lung cancer among nonsmokers exposed to environmental tobacco smoke primarily by studying lung cancer among non-smoking women married to smokers. Not all the studies have reported an excess risk linked to environmental tobacco smoke, but the great majority have. This consistency of findings across studies throughout the world establishes that exposure to environmental tobacco smoke is indeed associated with a small but a measurable increase in lung cancer.

Several additional features led the Science Advisory Board—myself included—to conclude that the relationship was likely to be causal, that is, that it was the environmental tobacco smoke that was responsible for the increase in lung cancer among passive smokers. First, virtually all the studies that examined dose response trends found rising risk of lung cancer with an increasing level of exposure to environmental tobacco smoke. The more the spouse smoked, the greater the risk to the nonsmoking partner. This is what would be expected if in fact environmental tobacco smoke were a carcinogen.

Second, there was no compelling evidence that the association was simply due to bias or due to confounding by other risk factors for lung cancer. Although only a few studies adjusted for dietary or other risk factors, those that did tended to show little change in the magnitude of the association between environmental tobacco smoke and lung cancer.

Third, increased risks of lung cancer were actually observed at exposure levels found in typical environmental studies. Thus, the risk assessment that was performed by EPA did not have to rely on extrapolations from high dose settings, as is sometimes done when relevant low-dose data are not available.

Finally, there is the biologic plausibility of the association. We know that cigarette smoking is a dominant cause of lung cancer in this country, and in fact in most others, with upwards of 20-fold excesses in risk in heavy smokers. Nonsmokers exposed to environmental tobacco smoke inhale many of the same substances that smokers do, although in smaller amounts.

Components of tobacco smoke have been detected in the blood and in the urine of nonsmokers with some of the carcinogenic compounds in tobacco bound to the hemoglobin of passive smokers. Thus, there is no doubt that tobacco components are absorbed and metabolized by environmental tobacco smoke-exposed nonsmokers.

There are quantitative differences in the chemical compositions of environmental tobacco smoke and inhaled cigarette smoke, but there are a great many qualitative similarities. It is therefore biologically plausible that this lower level of exposure to tobacco from environmental tobacco smoke results in an increased lung cancer risk.

There is uncertainty as to the extent of the increased risk and the exact number of cancer deaths among Americans that may result from passive smoking. Such imprecision is a common trait in epidemiological studies and reflects variations in sample sizes and other characteristics of the available data. Thus the estimate that 3,000 lung cancer deaths in the United States per year in the United States are due to environmental tobacco smoke exposure is reasonable, but it is an approximate figure.

The Science Advisory Board recommended that such uncertainty be recognized, but this did not alter our scientific judgment that prolonged exposure to environmental tobacco smoke can increase the risk of lung cancer. This was the fundamental conclusion drawn by EPA and also by reviews of the National Academy of

Sciences and the Surgeon General, and one with which the Science Advisory Board and myself fully concurred.

Thank you for this opportunity to come before you. I will be happy to answer any questions.

Senator LIEBERMAN. Thank you, Dr. Blot.

I would like to ask you a question that I am going to submit in writing to Dr. Coggins from the last panel because I want you to respond with what I thought was at the center of his critique of the EPA Study and some of the other allegations about the effect of secondhand smoke on people, his whole question of dose. In other words, perhaps the chemical components of the smoke that people inhale when they smoke and the chemical components of secondhand smoke are similar, but the dose is so different that it stretches the imagination to think that secondhand smoke could be such a determinant of cancer.

Dr. Coggins indicated in his testimony that the maximum amount of secondhand smoke to which a nonsmoker is exposed is equivalent to approximately one to four cigarettes per year. He said that was such a trivial dose that it is "scientifically implausible that they can result in meaningful toxicological activity".

I would say again that as a layman, the thought of one to four cigarettes a year doesn't sound like it could cause all the illness and disease and death that we have testified to. That is the top of the iceberg. Underneath is all this complicated statistical inquiry and methodology.

I gather that some of this may have to do with the physical extrapolation method that Dr. Coggins used, but I wanted to ask you to respond to those allegations because I think they go to the heart of what is at issue here.

Dr. BLOT. I think this equivalent of one to four cigarettes per year is definitely a minority view. It is the first time I have heard it. I think the evidence that is available suggests that the amount of exposure from environmental tobacco smoke in a nonsmoker—the actual levels experienced by nonsmokers—are much greater than that.

A comment that was made by Dr. Gravelle was that if you looked at levels of cotinine—which is a metabolite of nicotine—in nonsmokers who are exposed to environmental tobacco smoke compared to smokers, the ratio might be in the order of somewhere between 1 to 100 or 1 to 200. That is, nonsmokers have a much lower amount of cotinine in their body.

But if you figure that an average smoker smokes a pack a day of cigarettes and there are 365 days per year, and you multiply 20 times 365 and you take 1 percent of that—it is going to be a number much greater than the one to four cigarettes.

The problem in the extrapolations from biomarkers, as they are called, is that there are so many different compounds in cigarette smoke. There may be 4,000 different compounds. There are 40 or so carcinogens. The answer you get as to the relative exposure for a smoker compared to a nonsmoker exposed to environmental tobacco smoke depends upon which of these biomarkers you choose.

If you choose the extreme that Dr. Coggins mentioned, you will get this value which I think is not reasonable. If you take the cotinine level——

Senator LIEBERMAN. What is the extreme?

Dr. BLOT. That you get the equivalent of one to four cigarettes per year.

Senator LIEBERMAN. Are you familiar with the method used by Dr. Coggins?

Dr. BLOT. In general, the extrapolation method.

Senator LIEBERMAN. So am I hearing you correctly that you would say that the method used was not the appropriate method used? Or that it may be appropriate but one should not draw too firm a conclusion from it because there are other substances in smoke that may not have been measured?

Dr. BLOT. Right, and we really don't know what is the best measure of exposure. It could be cotinine; it could be one of the carcinogens in cigarette smoke. For example, there is a carcinogen called 4-aminobiphenyl. If you look at hemoglobin adducts to this particular carcinogen in smokers compared to passively exposed nonsmokers, the ratio is only seven to one. That is, smokers only have seven times more of this compound in their bodies than environmentally exposed nonsmokers.

So if it turns out that that was the relevant measure, then nonsmokers are getting the equivalent of one-seventh the exposure of smokers. If you figure that 20 cigarettes a day is average, one-seventh of that is about three cigarettes a day, not a year.

Senator LIEBERMAN. So, it is a dramatic difference. Dr. Coggins was suggesting maximum impact on a nonsmoker breathing in smoke as being one to four cigarettes a year. You are saying that under the method you have just described it could be as high as the effect of three cigarettes per day.

Dr. BLOT. Right. We really don't know for sure what it is. But there is this range. And what was cited earlier was the extreme low end in that range.

Senator LIEBERMAN. So is there any basis for concluding that the EPA Report is on the other extreme, or is it more balanced?

Dr. BLOT. The EPA recognized these problems in dealing with biomarkers and instead used the directly available epidemiological evidence. It has been mentioned several times today that there have been numerous studies—over 30 different studies—of lung cancer, and many more of childhood diseases, that actually measured risk associated with household exposure to environmental tobacco smoke. So we have some actual observable data.

If you summarize that data, it turns out that there is a small but measurable increase in risk of lung cancer among people who have lived with smokers, even though they don't smoke themselves.

Senator LIEBERMAN. Thank you for that answer.

Dr. Gravelle, to another element of the uncertainty of estimates, in your testimony you have discussed the uncertainty of EPA's methodology. To check the numbers, I believe you have indicated that you used the physical extrapolation method.

I wonder why you used that method to check EPA's analysis given the uncertainties associated with the method, which is to say, that it does not assess all the exposures that are parts of secondhand smoke.

Dr. GRAVELLE. We used it because while there are uncertainties in that method, there are also a lot of uncertainties in the statistical studies. We used cotinine itself because that is what the EPA used and all the literature that the EPA reviewed with one exception used the cotinine level. There was one study that used the respirable suspended particulate that Dr. Coggins talked about, which produced very small results.

This is not really my field, but it is clear that there are uncertainties about this method. The EPA used cotinine for a whole variety of corrections to their data. They used it for making a correction for classification error; they used it for extrapolating from the 500 direct deaths that you could estimate from the statistical evidence to the other 1,000 female never-smokers. In other words, most of the numbers in their study are from this kind of method.

It is within the group of passive rather than from active to passive. But that is certainly an approach they used and relied on and the cotinine measures are relied on to deal with a whole series of problems.

We are not saying that extrapolation is a perfect approach, but we are saying that we see some serious problems with the statistical studies. When you see serious problems, you want to go back and check it against alternatives.

Senator LIEBERMAN. Accepting that there are uncertainties in this method, why did you reach the conclusion that they overestimated? Isn't it possible that they could have underestimated the consequences of secondhand smoke?

Dr. GRAVELLE. The particular specification problems with the studies that were clearly identified were certainly in the direction that would overstate the effects; the misclassification issue and the confounding factors. Those would have both gone in the direction of reducing the estimate, in theory, had you been able to correct for them.

Senator LIEBERMAN. My time is up.

Senator Faircloth?

Senator FAIRCLOTH. Thank you, Mr. Chairman.

Senator Lieberman is going to bring this to a conclusion pretty fast, so if you will be extremely brief in your answers, I would appreciate it.

What is the mission of the Congressional Research Service? What is it supposed to do?

Dr. GRAVELLE. Our mission is to provide objective nonpartisan information to Congress.

Senator FAIRCLOTH. So when you all say something, it is right? You have no reason for it to be otherwise, right?

[Laughter.]

Dr. GRAVELLE. Absolutely. I have no other motive than to do research.

Senator FAIRCLOTH. Dr. Blot, I have been advised that the National Cancer Institute funded the Brownson and the Alavanja studies, the largest U.S. studies ever conducted on lung cancer in nonsmokers. My understanding is that the reason the Science Advisory Board of EPA did not insist on the inclusion of those studies in the EPA risk assessment is that the studies were not completed in time for the EPA analysis.

Were they completed in time?

Dr. BLOT. I think that is right. They were not ready in time.

Senator FAIRCLOTH. You think, but you are not sure?

Dr. BLOT. That is my impression, that they were not ready.

Senator FAIRCLOTH. That is what EPA said. However, under its guidelines EPA is required to address the existence of confounders, isn't it?

Dr. BLOT. Yes.

Senator FAIRCLOTH. Isn't this sound scientific practice?

Dr. BLOT. Yes.

Senator FAIRCLOTH. If EPA were conducting its own analysis today, wouldn't you recommend that those studies be included?

Dr. BLOT. Sure. Studies are continually being done. As time passes, we get new information all the time.

Senator FAIRCLOTH. Since OSHA is in the process of conducting its own risk assessment, you would advise them to include these studies, too?

Dr. BLOT. Yes.

Senator FAIRCLOTH. Do you have any children?

Dr. BLOT. Yes.

Senator FAIRCLOTH. Do you take them to the beach?

Dr. BLOT. Sometimes I do, yes.

Senator FAIRCLOTH. Aren't you exposing them to a high risk of cancer later on in life since many studies have indicated that children exposed to sun early have a high risk for cancer? Isn't that a dangerous thing you are doing with your children?

Dr. BLOT. Sunlight exposure is a risk factor for skin cancer and for melanoma, which can be fatal. When we go to the beach we attempt to take precautionary measures, including sunscreens to avoid burning.

Senator FAIRCLOTH. I understand that, but why not just stay home. We are closing down smoking because it carries a risk of cancer.

What about French fries at fast-food restaurants? Do you ever let your kids eat those?

Dr. BLOT. Sometimes my kids do, yes.

Senator FAIRCLOTH. Do you give them a stomach lining?

Dr. BLOT. I think the issue is whether or not we have enough evidence before us right now to declare that exposure to environmental tobacco smoke is harmful, and I think we do.

Senator FAIRCLOTH. I have one more question.

Are you married?

Dr. BLOT. Yes.

Senator FAIRCLOTH. Does your wife smoke?

Dr. BLOT. No, sir.

Senator FAIRCLOTH. If she did, would you divorce her?

[Laughter.]

Senator LIEBERMAN. You can plead the fifth here.

Dr. BLOT. I think it is unlikely that she would ever smoke cigarettes.

Senator FAIRCLOTH. That was not the question. If she did, would you divorce her?

Dr. BLOT. I don't know what would happen in that situation. It is unlikely that I would divorce her.

[Laughter.]

Senator FAIRCLOTH. The point I am making is clear. We have gone to angels dancing on needle points with this smoking. We are completely ignoring every other risk factor for cancer. At the beach, you take your children. As Dr. Taylor said earlier, he did not want his grandchildren to go to a restaurant because there was smoke in it. I assume they go to the beach because most do. So we are taking one issue and making it the whipping boy and we are lightly going like a blinded and deafened horse to the battle on every other cancer issue.

You talk about putting a 60 cent sun lotion on your children and take them to the beach and it doesn't concern you, yet—and I don't mean you, but people of your mind set—go into a spasm if you go into a restaurant and there is smoking in one dark corner of it.

I think we ought to be fair.

I thank you.

Senator LIEBERMAN. Thank you, Senator Faircloth.

We are trying hard to assess different forms of threat to the American people. I do want to say, Dr. Blot, that I am reassured that your marriage has survived the threats that may have been placed on it.

[Laughter.]

Senator LIEBERMAN. Senator Lautenberg?

Senator LAUTENBERG. Thank you very much.

Do you drag your kids to the beach and just pull them along over the curbs and all that to get them down to the beach, or do they voluntarily go?

Mr. BLOT. It is voluntary.

Senator LAUTENBERG. So what happens when they are in a room with smokers? Do they get a chance to voluntarily block it out, or do they just have to take what is in there?

Mr. BLOT. They might not get that voluntary chance.

Senator LAUTENBERG. My kids go to the beach. I try to convince them to cover up. I try to convince them not to take the unnecessary risk and to make their own independent decisions as to what to do.

Dr. Gravelle, one of the things that concerns me—you admitted that you are both economists. So here we are, three of us in an unscientific science, although my education is not as extensive as yours.

You have medical science people in CRS, do you not?

Dr. GRAVELLE. That is correct.

Senator LAUTENBERG. Why didn't they do the response to the report?

Dr. GRAVELLE. The passive smoking issue in our cigarette tax paper was a fairly minor subset of a lot of other things that we did. We consulted very closely with them. The report was read and approved and I spent a lot of time with the science policy division doing this report.

Senator LAUTENBERG. They weren't asked to write the analysis of the EPA study?

Dr. GRAVELLE. There is just a small part of this paper on cigarette taxes that had to do with passive smoking.

Senator LAUTENBERG. So it was focused primarily on the tax issue. Were the assumptions about the risk essential to the determination on what revenues might flow from the taxes?

Dr. GRAVELLE. We looked at revenue yield, we looked at the price elasticity, we looked at the path of revenue over time—we did all those things. But the part of the paper that this was related to was really measuring spill-over costs and trying to compare those to existing cigarette taxes. One of the spill-overs, obviously, that we had to look at was the passive smoking issue.

Senator LAUTENBERG. So was the assertion that the methodology might not have been precise in your view—did you have to make the case by getting to the health effects? If you were interested in the financial yield on this, then I am trying to understand why it is that we got into the question of whether or not their health effects analysis was accurate.

Dr. GRAVELLE. As you know, one of the efficiency issues you would look at in doing an economic analysis is whether smokers are having the right sort of price signals when they buy cigarettes. Part of the price signals are effects they have on other people that are not priced. There are lots of different kinds of effects we looked at. Direct health care costs of smokers was one on which we spent a lot of time. One aspect of that that we thought was crucial to that analysis was the passive smoking effect.

Senator LAUTENBERG. So you are saying that the net yield—because the savings might not have been there as a result of non-ill health effects——

Dr. GRAVELLE. There are two basic kinds of spill-over effects. One is the potential medical effects basically because we charge the same insurance premiums and don't differentiate by smoking status. That is one effect. You have to look at that over a whole lifetime. The second effect would be the passive smoke.

We talked about other things also, such as annoyance and all the things we could think of and measured all the things we could try to measure. There is a whole series of issues we looked at.

Senator LAUTENBERG. I am going to commission a study by CRS on annoyance and see how much that costs the Government.

Dr. GRAVELLE. That one is hard to measure.

Senator LAUTENBERG. Was your CRS report peer reviewed by outside experts in any way?

Dr. GRAVELLE. In general, the process through which we go in receiving requests, answering requests, and reviewing requests is confidential at the wish of Congress. I will say that we have internal review in our subject area. We have internal review in the cross-disciplinary subject areas, other subject areas that are relevant to our studies. We have internal review and external review when it is appropriate.

As you know, we handle thousands and thousands of requests every year, so there is not a consistent review process. I would say that there is a good look at the study from lots of sources, including congressional sources, non-congressional sources, and discussions we carried on with people. It was a very carefully examined study, in my view.

Senator LAUTENBERG. It didn't have the same type for the reasons stated as far as peer review as did the EPA study.

Dr. GRAVELLE. We have no regulatory authority. We have no influence on the regulatory authority. Of course, if there were to be criticisms after a paper is released that we thought were valid we would certainly change our papers. We have done that before every once in awhile. In answering a lot of questions, you make a mistake. There is no problem with that.

Senator LAUTENBERG. Have you had any criticism related to your observations?

Dr. GRAVELLE. No, sir.

Senator LAUTENBERG. The EPA Administrator stated, and several other people, that she believes the environmental tobacco smoke can cause as many as 3,000 lung cancer deaths a year. You suggest that there might only be 600 deaths per year related to environmental tobacco smoke.

Therefore, in your comments you say, "Our evaluation was that the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking."

How much more than 600 deaths does it have to be to get to be substantial?

Dr. GRAVELLE. I guess substantial is sort of in the eyes of the beholder. We can even take the EPA numbers with the 3,000 deaths. I would characterize that as a small risk, perhaps you wouldn't. They are in the same general magnitude of the risk of driving a small car instead of a large car.

The lifetime risk is in the neighborhood of 0.1 percent to 0.2 percent. The chance of dying is 100 percent. So compared to many other risks—we face risks all the time. that is one of the things about economics that I think is very valuable in looking at this subject. People do face risks of all sorts of different types all the time. We live risky lives.

The question I think is, What risk do you want to correct at what cost? Is it worth it? Is it large enough?

Senator LAUTENBERG. If it is my kid, it is large enough, I can tell you that. Also, I make sure that my children—they are adults now, but my grandchild—that they use seat belts. The risk of dying in a car accident compared to the number of miles driven each day is pretty darned small. But why take the extra risk if you don't have to?

Why should those extra 600 or 3,000 people—why should we take that risk if we don't have to? Aren't we obliged to protect the public health? It is alleged that much of this risk is to small children and that the 150,000 incidents a year of some asthmatic response to smoke—are those insubstantial risks in your mind?

Dr. GRAVELLE. We calculated in our paper the only number we could come up with in terms of translating it to a cigarette tax concerning the medical cost of hospitalization, which I think was about 1 cent to 3 cents per pack.

There are a couple of observations you can make about children. A lot of this is going to occur in the home with the parents, if it does occur. a place that I think is beyond the reach of regulation.

Senator LAUTENBERG. But now you are getting into the health analysis side of things, which you said that you didn't want to do.

Dr. GRAVELLE. I said that I think that is beyond the reach of regulation.

Senator LAUTENBERG. I understand. But you also said that it is largely in the home.

But the fact is that when we look at the preventable risk of people developing disease or having a problem with their health as a result of the exposure, we have to somehow or another separate it from the pure financial analysis. Thank you.

Thank you very much, Mr. Chairman.

Senator LIEBERMAN. Thank you, Senator Lautenberg.

I would like to follow up with just one question based on what Senator Lautenberg was just asking you.

It was my understanding that in the financial impact analysis that you made, you focused on the lung cancer deaths and did not include the conclusions in the EPA report about the impact on children with bronchitis, middle ear infections, and all the rest. Is that correct.

Dr. GRAVELLE. As I said, we looked at the only one we could make some sort of attempt to quantify, and the one they stressed a great deal. Numbers like 3,000 look big, but in a country where 2 million people die every year and where there are 260 million people or so—it is not big.

Senator LIEBERMAN. All I want to point out for the sake of clarity is that the numbers you presented were based on the lung cancer deaths.

Dr. GRAVELLE. About the cigarette tax?

Senator LIEBERMAN. Yes.

Dr. GRAVELLE. We tried to do extrapolations for all the adult diseases.

Senator LIEBERMAN. What about for the kids?

Dr. GRAVELLE. With the kids, we looked at the numbers we could come up with.

Senator LIEBERMAN. So you did try to include it?

Dr. GRAVELLE. To the extent that we could try to quantify it. Some things just can't be quantified.

Senator LIEBERMAN. The 150,000 to 300,000 cases of bronchitis, pneumonia, and hospitalizations?

Dr. GRAVELLE. Yes, we looked at those.

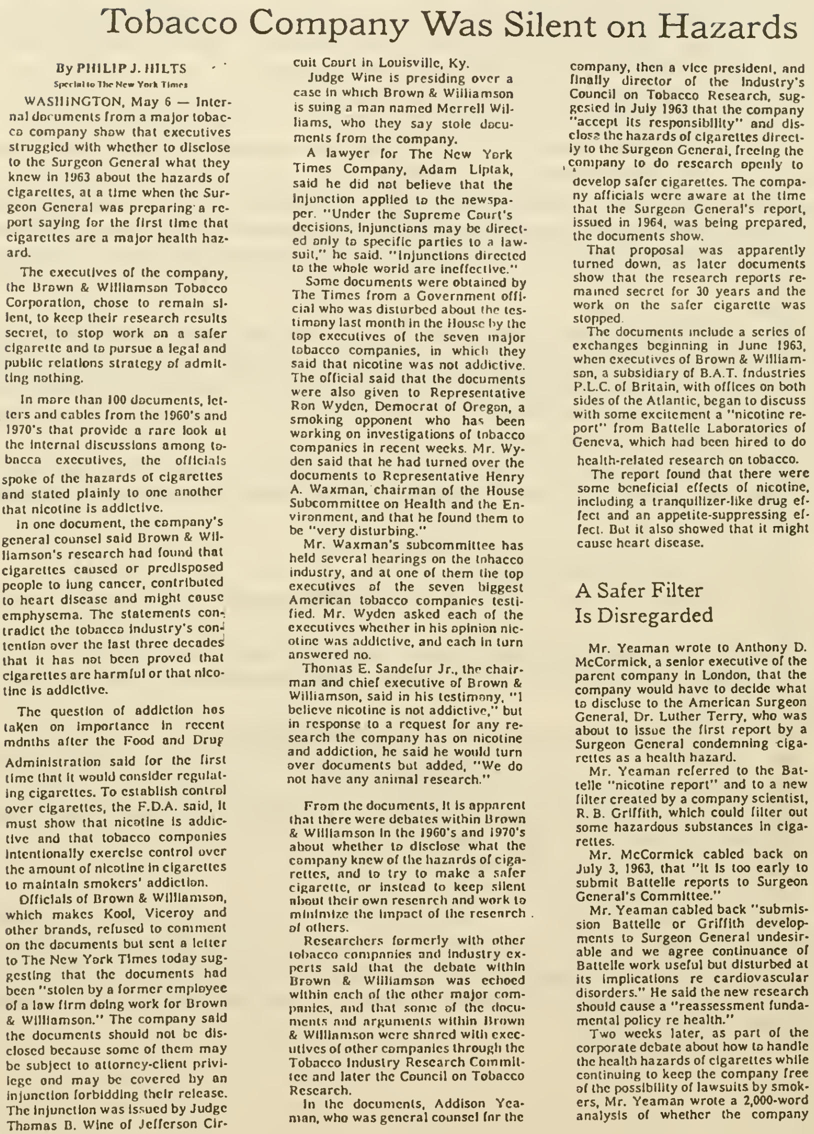
Senator LIEBERMAN. I thank all of you.

Senator LAUTENBERG. I would like to have inserted into the record an article that appeared in the New York Times on Saturday, May 7th, entitled, "Tobacco Company was Silent on Hazards".

Senator LIEBERMAN. Without objection, the referenced article will appear in the record.

[The article follows:]

[From the New York Times, May 7, 1994]



Tobacco Company Was Silent on Hazards

By PHILIP J. HILTS

Special to The New York Times

WASHINGTON, May 6 — Internal documents from a major tobacco company show that executives struggled with whether to disclose to the Surgeon General what they knew in 1963 about the hazards of cigarettes, at a time when the Surgeon General was preparing a report saying for the first time that cigarettes are a major health hazard.

The executives of the company, the Brown & Williamson Tobacco Corporation, chose to remain silent, to keep their research results secret, to stop work on a safer cigarette and to pursue a legal and public relations strategy of admitting nothing.

In more than 100 documents, letters and cables from the 1960's and 1970's that provide a rare look at the internal discussions among tobacco executives, the officials spoke of the hazards of cigarettes and stated plainly to one another that nicotine is addictive.

In one document, the company's general counsel said Brown & Williamson's research had found that cigarettes caused or predisposed people to lung cancer, contributed to heart disease and might cause emphysema. The statements contradict the tobacco industry's contention over the last three decades that it has not been proved that cigarettes are harmful or that nicotine is addictive.

The question of addiction has taken on importance in recent months after the Food and Drug Administration said for the first time that it would consider regulating cigarettes. To establish control over cigarettes, the F.D.A. said, it must show that nicotine is addictive and that tobacco companies intentionally exercise control over the amount of nicotine in cigarettes to maintain smokers' addiction.

Officials of Brown & Williamson, which makes Kool, Viceroy and other brands, refused to comment on the documents but sent a letter to The New York Times today suggesting that the documents had been "stolen by a former employee of a law firm doing work for Brown & Williamson." The company said the documents should not be disclosed because some of them may be subject to attorney-client privilege and may be covered by an injunction forbidding their release. The injunction was issued by Judge Thomas B. Wine of Jefferson Circuit Court in Louisville, Ky.

Judge Wine is presiding over a case in which Brown & Williamson is suing a man named Merrell Williams, who they say stole documents from the company.

A lawyer for The New York Times Company, Adam Liptak, said he did not believe that the injunction applied to the newspaper. "Under the Supreme Court's decisions, injunctions may be directed only to specific parties to a lawsuit," he said. "Injunctions directed to the whole world are ineffective."

Some documents were obtained by The Times from a Government official who was disturbed about the testimony last month in the House by the top executives of the seven major tobacco companies, in which they said that nicotine was not addictive. The official said that the documents were also given to Representative Ron Wyden, Democrat of Oregon, a smoking opponent who has been working on investigations of tobacco companies in recent weeks. Mr. Wyden said that he had turned over the documents to Representative Henry A. Waxman, chairman of the House Subcommittee on Health and the Environment, and that he found them to be "very disturbing."

Mr. Waxman's subcommittee has held several hearings on the tobacco industry, and at one of them the top executives of the seven biggest American tobacco companies testified. Mr. Wyden asked each of the executives whether in his opinion nicotine was addictive, and each in turn answered no.

Thomas E. Sandefur Jr., the chairman and chief executive of Brown & Williamson, said in his testimony, "I believe nicotine is not addictive," but in response to a request for any research the company has on nicotine and addiction, he said he would turn over documents but added, "We do not have any animal research."

From the documents, it is apparent that there were debates within Brown & Williamson in the 1960's and 1970's about whether to disclose what the company knew of the hazards of cigarettes, and to try to make a safer cigarette, or instead to keep silent about their own research and work to minimize the impact of the research of others.

Researchers formerly with other tobacco companies and industry experts said that the debate within Brown & Williamson was echoed within each of the other major companies, and that some of the documents and arguments within Brown & Williamson were shared with executives of other companies through the Tobacco Industry Research Committee and later the Council on Tobacco Research.

In the documents, Addison Yeaman, who was general counsel for the company, then a vice president, and finally director of the industry's Council on Tobacco Research, suggested in July 1963 that the company "accept its responsibility" and disclose the hazards of cigarettes directly to the Surgeon General, freeing the company to do research openly to develop safer cigarettes. The company officials were aware at the time that the Surgeon General's report, issued in 1964, was being prepared, the documents show.

That proposal was apparently turned down, as later documents show that the research reports remained secret for 30 years and the work on the safer cigarette was stopped.

The documents include a series of exchanges beginning in June 1963, when executives of Brown & Williamson, a subsidiary of B.A.T. Industries P.L.C. of Britain, with offices on both sides of the Atlantic, began to discuss with some excitement a "nicotine report" from Battelle Laboratories of Geneva, which had been hired to do health-related research on tobacco.

The report found that there were some beneficial effects of nicotine, including a tranquilizer-like drug effect and an appetite-suppressing effect. But it also showed that it might cause heart disease.

A Safer Filter Is Disregarded

Mr. Yeaman wrote to Anthony D. McCormick, a senior executive of the parent company in London, that the company would have to decide what to disclose to the American Surgeon General, Dr. Luther Terry, who was about to issue the first report by a Surgeon General condemning cigarettes as a health hazard.

Mr. Yeaman referred to the Battelle "nicotine report" and to a new filter created by a company scientist, R. B. Griffith, which could filter out some hazardous substances in cigarettes.

Mr. McCormick cabled back on July 3, 1963, that "It is too early to submit Battelle reports to Surgeon General's Committee."

Mr. Yeaman cabled back "submission Battelle or Griffith developments to Surgeon General undesirable and we agree continuance of Battelle work useful but disturbed at its implications re cardiovascular disorders." He said the new research should cause a "reassessment fundamental policy re health."

Two weeks later, as part of the corporate debate about how to handle the health hazards of cigarettes while continuing to keep the company free of the possibility of lawsuits by smokers, Mr. Yeaman wrote a 2,000-word analysis of whether the company should acknowledge the hazards of cigarettes and accept the risks of litigation, or say nothing, but give up the ability to talk about its research in public and give up credible standing to analyze and criticize the Surgeon General's report.

Mr. Yeaman said in the report, labeled "strictly private and confidential" and dated July 17, 1963, that the new information about the tranquilizing effects of nicotine and its positive effects on weight loss "delivers to the industry what may well be the first effective instrument of propaganda counter to that of the American Cancer Society, et al, damning cigarettes as having a causal relationship to cancer of the lung."

He said the positive nicotine findings and the Griffith filter were "a bridge over which the industry could pass from its present terrain of defense to a field for effective counterattack." The Griffith filter could selectively take hazardous substances out of cigarette smoke, but could leave the good taste and the nicotine. This device would provide the opening politically, and the positive uses of nicotine would be their "weapon."

He noted that company research had shown that nicotine has a tranquilizing, or anxiety-reducing effect, and helps control body weight, and "moreover, nicotine is addictive."

"We are, then, in the business of selling nicotine, an addictive drug effective in the release of stress mechanisms," he wrote.

The research found that despite the beneficial effects of nicotine, cigarettes "cause, or predispose, lung cancer."

"They contribute to certain cardiovascular disorders," the research found. "They may well be truly causative in emphysema, etc. etc."

Anticipated Report By Surgeon General

The memo said that the Surgeon General would soon issue a major report that would conclude that cigarettes cause lung cancer and cardiovascular disease.

The industry, he said, should take the event seriously. Whatever means the companies used to minimize the impact of the Surgeon General's report, the industry must face the fact that a "responsible and qualified group of previously non-committed medical authorities have spoken," he wrote.

Mr. Yeaman said the company should not continue to say that the hazards were not proved, and should not continue in a defensive posture. Rather, he said, the industry should embark on a "massive and impressively financed" campaign of research that would either disprove the hazard, or far more likely, he said, discover just which chemicals are the cancer-causing ones so the companies could "neutralize them."

He dismissed the possibility that the work could be conducted by the Tobacco Institute Research Committee, which in January 1954 the industry told consumers in full-page newspaper advertisements would do such research. Mr. Yeaman acknowledged to his colleagues that the research council "was conceived as a public relations gesture and (however undefiled the Scientific Advisory Board and its grants may be) it has functioned as a public relations operation."

He envisioned a large research institute which asked for the help of the American Cancer Society and other major organizations concerned with public health, and would be a new organization "lavishly financed, autonomous, self-perpetuating and uncontrolled" by the industry.

This bold move in which the industry would "accept its responsibility" would actually free the company to take a "much more aggressive posture to meet attack." He acknowledged that it might worsen the industry's position in lawsuits, but that risk would be worth it because of the greater benefit of being on the attack.

He noted that this advice was very different from what he had said up to that time, but that it was not really inconsistent. If the industry did not want to take on the responsibility for health research, it should remain largely silent.

Mr. Yeaman said that while the industry contemplated this long-term strategy, it would have to deal with the Surgeon General and antismoking groups and Congressmen when the Surgeon General's report was issued.

He accurately predicted that there would be a wave of attempts to educate the public about smoking hazards, particularly the young, that there would be an effort to ban smoking ads on television and radio, that labels warning of the hazards of smoking would be put on cigarette packs, and that cigarette taxes would shoot up.

The difficulty of being open with the Government was that juries might realize that the companies knew of the hazards, had the means to make a safer cigarette, but did not do so. The jurors, he said, might have an "emotional reaction" and go against the companies.

He proposed, finally, that the industry should challenge whatever parts of the Surgeon General's report they could, announce the creation of a new tobacco research institute, and announce "our triple, or quadruple or quintuple filter, capable of removing whatever constituent of smoke is currently suspect while delivering full flavor — and incidentally — a nice jolt of nicotine."

"And if we are the *first* to be able to make and sustain that claim," the memo said, "what price Kent?"

Mr. Yeaman, reached at his home in Louisville, said he would not discuss his memorandums over the phone.

In the years since Mr. Yeaman's analysis, several tobacco companies have created cigarettes which can greatly reduce the amounts of key disease-causing chemicals, which can nearly eliminate second-hand smoke, and which can nearly eliminate the fire hazard of cigarettes. None are currently on the market.

Senator LIEBERMAN. I thank Dr. Gravelle and Dr. Blot and all the other witnesses. I think this has been a very informative hearing. Obviously, there are different points of view, which is what we wanted to expose here and discuss. But I do think that we have established a good factual record for us to consider as we move these bills through this Congress. I thank you all for participating and helping us in that way.

The record of the hearing will remain open for 3 weeks so that we may submit additional questions to you if we would like, and you may add to your testimony if you would like.

I thank all of you.

The hearing is adjourned.

[Whereupon, at 12:53 p.m., the subcommittee was adjourned, to reconvene at the call of the Chair.]

[Statements submitted for the record and bills S. 262 and S. 1680 follow:]

STATEMENT OF HON. CAROL M. BROWNER, ADMINISTRATOR, ENVIRONMENTAL PROTECTION AGENCY

Good morning, Mr. Chairman and Members of the Subcommittee. I am pleased to be here to testify on the Environmental Protection Agency's (EPA) activities related to environmental tobacco smoke, to comment on S. 1680, the Smoke-Free Environment Act of 1993, and to summarize for you our conclusions concerning the economic impacts of smoking restrictions in the United States.

Environmental tobacco smoke (ETS), also called secondhand smoke, is a mixture of the smoke given off by the burning end of a cigarette, pipe, or cigar and the smoke exhaled from the lungs of smokers. This mixture contains more than 4,000 substances, many of which are strong irritants, and more than 40 of which are known or suspected human carcinogens. Exposure to secondhand smoke is called involuntary smoking or passive smoking.

In January 1993, the Environmental Protection Agency (EPA) released an assessment of the respiratory health risks of passive smoking, titled "Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders." This report was issued under the authority of The Radon Gas and Indoor Air Quality Research Act of 1986, which directs EPA to conduct research and disseminate information on all aspects of indoor air quality. The report summarizes the findings of the Agency's comprehensive investigation of the respiratory health risks from exposure to ETS. It incorporates comments and recommendations from the public, as well as two reviews by EPA's Science Advisory Board, a panel of independent scientific experts in this field. The Science Advisory Board concurred in the methodologies employed and unanimously endorsed the conclusions of the report. The Department of Health and Human Services (HHS) has endorsed the report and the National Cancer Institute within HHS printed it as one of its series of scientific monographs.

Based on the total weight of the available scientific evidence, EPA concluded that the widespread exposure to secondhand smoke in the United States presents a serious and substantial public health risk. I will briefly summarize the findings of the risk assessment.

Findings of the EPA Risk Assessment

Perhaps the most significant conclusion of the report is the finding that environmental tobacco smoke is a human lung carcinogen, classified as a Group A carcinogen under EPA's carcinogen assessment scheme. This classification is reserved for those compounds or mixtures that have the strongest evidence of a cause-and-effect relationship in humans. Only 16 compounds have received this designation. In the case of ETS, unlike any other compound the Agency has ever evaluated , we are able to see a consistent increase in human cancer risk at typical environmental levels, rather than extrapolating downward from very high occupational exposures, as we have had to do for such other Group A carcinogens as asbestos and benzene. Also, using these studies at typical environmental levels, EPA estimated that secondhand smoke is responsible for approximately 3,000 lung cancer deaths per year in non-smokers in the United States. Of these 3,000 annual lung cancer deaths, the

EPA estimates that approximately 2,200 are attributable to exposure outside the home.

Environmental tobacco smoke causes other significant effects on the respiratory health of adult non-smokers. These include coughing, phlegm production, chest discomfort, and reduced lung function.

Although the finding that ETS is capable of causing lung cancer in healthy adults is extremely significant, I am personally very concerned about the very serious respiratory effects on young children—who are particularly sensitive to the effects of secondhand smoke—that are documented in our report.

Infants and young children whose parents smoke are at increased risk of lower respiratory tract infections such as pneumonia and bronchitis. In the risk assessment, EPA estimates that passive smoking is responsible for between 150,000 and 300,000 lower respiratory tract infections per year in infants and children under 18 months of age, resulting in between 7,500 and 15,000 hospitalizations each year.

Children who have been exposed to secondhand smoke are also more likely to have reduced lung function and symptoms of respiratory irritation such as cough, excess phlegm, and wheezing. In addition, passive smoking can lead to a buildup of fluid in the middle ear, the most common cause of hospitalization of children for an operation.

Asthmatic children are especially at risk. EPA estimates that exposure to environmental tobacco smoke increases the number of episodes and the severity of symptoms for between 200,000 and one million asthmatic children every year. Moreover, passive smoking is a risk factor for the thousands of non-asthmatic children who develop the condition.

EPA's conclusions on the respiratory health effects of passive smoking confirm and strengthen those of earlier assessments by the U.S. Surgeon General (1986) and the National Research Council of the National Academy of Sciences (1986). The National Institute of Occupational Safety and Health (1991) concluded that occupational exposure to ETS causes increased risks of lung cancer and probably heart disease. The position of the National Cancer Institute (1993) is that ETS is a proven cause of lung cancer in non-smoking adults and is associated with an increased risk of coronary heart disease.

Policy Recommendations

EPA firmly believes that the scientific evidence is sufficient to warrant actions to protect people from involuntary exposure to environmental tobacco smoke.

Because of the health implications of exposure to ETS documented in our risk assessment, EPA has recommended actions to help parents, decisionmakers, and building occupants prevent involuntary exposure to secondhand smoke. EPA's primary recommendations are that:

- Residents not smoke in their home or permit others to do so.
- Every organization dealing with children—schools, day care facilities, and other places where children spend time—have a smoking policy that effectively protects children from exposure to environmental tobacco smoke.
- In the workplace, EPA recommends that every company have a smoking policy that effectively eliminates involuntary exposure to environmental tobacco smoke, either through complete bans or by limiting smoking to rooms that are specially designed to prevent smoke from escaping to other areas of the building.
- Employer-supported smoking cessation programs should be a part of any smoking policy.
- If smoking is permitted in a restaurant or bar, placement of smoking areas should take into account the ventilation characteristics of the space, to minimize involuntary exposure.

We believe it is our responsibility to help educate the public about the hazards to health from secondhand smoke and actions they can take to prevent involuntary exposure. We believe we are making progress in the effort. In less than a year, we have distributed almost half a million copies of our brochure, "What You Can Do About Secondhand Smoke," which explains in detail the recommendations I just listed.

EPA recently took part in a survey conducted in conjunction with the Conference of Radiation Control Program Directors (CRCPD), to assess the awareness of secondhand smoke and radon, as well as radon testing and mitigation rates, in the United States. More than 30,000 adults were surveyed about their knowledge of secondhand smoke. Ninety-five per cent of those surveyed had heard of secondhand smoke, and fully 86 percent of those believe it is unhealthy. Of the total sample, 82 percent say ETS is unhealthy, while only 9 percent disagree and say it has little or no effect on health. We believe the results of this survey can be extrapolated to the population as a whole. Indeed, according to a recent New York Times/CBS News survey of 1,215 adults, two-thirds of those responding to the poll favor a smoking ban in all public places.

EPA is working closely with public and private sector partners to continue to educate the public about secondhand smoke and actions that can protect people from the health risks associated with ETS exposure. In cooperation with the American Lung Association, EPA is focusing on high risk audiences who are more likely to be exposed to secondhand smoke. We are also working with the American Medical Association and the National Medical Association to educate their members and, in turn, their patients, about the health effects from secondhand smoke and what they can do to prevent exposure. EPA coordinates closely with the HHS Office on Smoking and Health on their public information efforts, and we are working with a wide range of state and local government agencies to educate the public about the hazards of secondhand smoke.

Many Federal agencies, state and local governments and private sector organizations have begun to implement some form of smoking restrictions indoors as a result of the landmark reports issued in 1986 by the U.S. Surgeon General and the National Research Council of the National Academy of Sciences. Since publication of the EPA risk assessment on passive smoking, however, we have seen a rapid acceleration of measures to prevent involuntary exposure in a variety of settings, including workplaces, restaurants, sporting facilities, health and day-care facilities, shopping centers, and a wide range of other public facilities. It is estimated that about 23 percent of the U.S. population is effectively covered by restrictive smoking policies.

Despite this encouraging trend, there are many places where involuntary exposure to secondhand smoke still occurs. Many businesses are concerned about being left at a competitive disadvantage if they go smoke-free, or if their communities enact restrictive smoking ordinances and neighboring jurisdictions do not. While recent studies of the effects of local ordinances on revenues and the experiences of many businesses suggest that smoking restrictions do not reduce sales or revenues for businesses that choose to adopt them—in fact, many report increases in commerce and revenue—businesses frequently receive misinformation claiming that smoking restrictions will hurt their business.

ADMINISTRATION VIEWS ON PENDING LEGISLATION

S. 1680—Smoke-Free Environment Act of 1993

The Smoke-Free Environment Act of 1993, S. 1680, would prohibit the smoking of tobacco products within any building regularly entered by ten or more persons at least one day per week, including Federal, state, and local government buildings. In lieu of a smoking ban, the bill would allow smoking in designated areas that ensure that air from the smoking area is exhausted directly to the outside and does not drift to other areas of the facility.

Most importantly, passage of S. 1680 would provide comprehensive protection from involuntary exposure to ETS in indoor environments to all persons, including children, workers, and the general public.

It would also produce a number of important secondary benefits. First, studies indicate that smoking restrictions in some cases can help encourage smokers to quit or cut back and discourage nonsmokers from starting.

For smokers who live in homes with high levels of another indoor air pollutant—radon—quitting smoking greatly reduces their risk of lung cancer from exposure to radon, which is ten times greater for smokers than for nonsmokers. The benefits of reducing smoking in terms of improved health and longer lives are significant.

In addition, Federal legislation in this area would level the playing field for businesses that are concerned—correctly or incorrectly—about any potential competitive disadvantage that could result from strong smoking restrictions.

S. 1680 would not, however, attempt to control individual behavior in the home, nor would it prohibit people who choose to smoke from doing so in most outdoor locations or in buildings that provide properly designed smoking rooms, and we think this is appropriate. The focus of this legislation is to prevent involuntary exposure to environmental tobacco smoke in public facilities.

The Administration agrees with and appreciates the fact that section 504 of S. 1680 does not place the burden of enforcing the bill solely on the Federal government, since the burden of such an enforcement program, if placed solely on the Federal government, could be severe.

It is important to recognize that the Occupational Safety and Health Administration (OSHA) has a central role to play on all safety and health issues in the workplace, under the Occupational Safety and Health (OSH) Act. Because of OSHA's role in regulating the workplace, further discussion between the Federal agencies involved and this Subcommittee may be warranted.

We support this bill and we look forward to working with the Subcommittee over specific concerns as the bill is debated.

S. 262—Protecting Our Federal Building Workers and Visitors From Exposure To Deadly Smoke (PRO-FEDS) Act of 1993

S. 262, the Preventing Our Federal Building Workers and Visitors From Exposure to Deadly Smoke (PRO-FEDS) Act of 1993, would establish smoking policies in all Federally owned or leased buildings. The Act would prohibit smoking or provide for separately ventilated smoking areas at each Federal agency, United States Courts, and Legislative Branch building. This is an excellent step toward protecting our Federal employees and people who occupy Federal buildings from involuntary exposure to environmental tobacco smoke.

The general thrust of S. 262 represents responsible governmental action for protecting public health and provides a model for state and local governments to follow.

Costs and Benefits of H.R. 3434

Congressman Henry Waxman, the chief sponsor of H.R. 3434, companion bill to S. 1680, and Chairman of the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, requested that EPA analyze the economic costs and benefits of H.R. 3434. Analysis of eight specific issues was requested. I provided our preliminary findings to Mr. Waxman's Subcommittee in February, and the full report was transmitted on April 21.The analysis accounts for the benefits and costs associated with policies in H.R. 3434 and S. 1680 that restrict smoking in virtually all indoor environments outside the home. Our analysis indicates that such restrictions could achieve net benefits ranging from $39 billion to $72 billion per year excluding some potentially significant costs and benefits to smokers.

EPA estimates that the total cost of implementing smoking policies in the United States would range from $0.5 billion to $1.4 billion per year. This is comprised of $0.1 billion to $0.4 billion per year for implementing smoking bans; $0.3 billion to $0.7 billion per year for constructing smoking areas; and $0.1 billion to $0.4 billion per year for enforcement.

The analysis indicates that passage of S. 1680 could achieve benefits ranging from $39 billion to $72 billion per year. Major benefits include those associated with reduced involuntary exposure to environmental tobacco smoke ($35 billion to $65 billion per year) and reduced operating and maintenance expenses in buildings ($4 billion to $8 billion per year). Other benefits include savings from reduced absenteeism ($0.2 billion to $0.3 billion per year) and reduced smoking-related fire injuries and losses ($0.5 to $0.7 billion per year).

Some anticipated effects of legislation such as S. 1680 or H.R. 3434 were not quantified. These include an expected increase in productivity and improved comfort of smokers and nonsmokers from reduced exposure to ETS, and an expected decrease in productivity. They also include losses in terms of time and convenience associated with forcing smokers to shift the location and/or timing of their cigarette consumption, and the potential burden associated with quitting.

In addition, for a number of reasons, the monetary value of direct health benefits to smokers was not quantified. These include the value of reduced premature deaths caused by smoking. The Centers for Disease Control and Prevention estimates that smoking causes more than 400,000 premature deaths per year to smokers. The EPA analysis suggests that, by enacting S. 1680 or H.R. 3434, between 27,000 and 54,000 per year premature deaths would be avoided on average in each of the first 50 years, and between 47,000 to 92,000 would be avoided each year thereafter.

EPA's analysis of H.R. 3434 was reviewed by the Office of Management and Budget, the Council of Economic Advisors, the Department of Health and Human Services, and several independent economists. Notice of the availability of the analysis for public review and comment will appear in the Federal Register shortly.

On balance, there appears to be substantial economic justification in support of S. 1680 and H.R. 3434, based on the specific cost and benefit issues addressed in our analysis. But the benefits of smoking restrictions such as those embodied in S. 1680 and H.R. 3434 go far beyond mere dollars. Smoking is one of the most dangerous causes of illness in America—and one of the most preventable. Smoking restrictions would reduce premature deaths among smokers and nonsmokers. They would improve health—especially children's health—resulting in fewer cases of respiratory illness, ear infections, and asthma.

Cigarettes don't just kill people who smoke. They also kill people who choose not to smoke. We have a responsibility to protect children and adults from involuntary exposure to other peoples' smoke.

This concludes my prepared testimony. I would be pleased to respond to any questions you may have.

STATEMENT OF M. JOYCELYN ELDERS, SURGEON GENERAL, U.S. PUBLIC HEALTH SERVICE

Good morning!

In February, I had the pleasure of appearing with five of the former Surgeons General before Chairman Waxman on the issue before us today—the health consequences of environmental tobacco smoke. Each one of us cited the extensive science base that supports one undeniable fact—environmental tobacco smoke is a very real environmental hazard, particularly to our most vulnerable citizens, our children.

Today I am equally pleased to be here to applaud your efforts, Chairman Lieberman and Senator Lautenberg, to bring this issue to the Senate. Your efforts on this bill, and, Senator Lautenberg, your effort on the recently enacted PRO-Kids provision of the Goals 2000 Educate America Act, will do more to protect our children than anything else we can do.

Now let me turn to the issue at hand. Picture with me for a moment a room full of preschoolers, each with a cigarette in their mouths. In essence, this is what we are doing to our children every time we expose them to secondhand smoke. *It has toxic and carcinogenic effects that are very similar to mainstream smoke.* When we smoke around our children, then, our children are smoking.

Indeed, we are all affected by secondhand smoke. Asthma, bronchial problems, and the future risk of lung cancer are as real in adults as they are in children, but the fact is children, especially young children, are more vulnerable to this harm. Not only are they physically vulnerable, but our children are also vulnerable because they are held captive to adult management of their spaces. Unlike adults, they cannot negotiate for smoke-free environments, and, unlike adults, they cannot simply get up and leave.

Let me review a few of the facts:

- Nine million American children under the age of five are exposed to secondhand smoke in their homes.
- Nearly 800,000 children in the United States are exposed to secondhand smoke in their childcare centers or schools.
- Many other children each day are forced to breath air polluted with cigarette smoke in automobiles, shopping malls, and restaurants—particularly fast food restaurants that cater to children.
- Exposure to secondhand smoke causes up to 300,000 lower respiratory tract infections each year in children less than one and a half years old.
- These needless infections result in up to 15,000 hospitalizations yearly.
- ETS exposure is a risk factor for asthma and causes increased severity of symptoms in children with asthma.
- A recent study from the Center for Disease Control and Prevention's National Center for Health Statistics found that infants are three times more likely to die from Sudden Infant Death Syndrome (SIDS) if their mothers smoke during and after pregnancy than those infants whose mothers do not smoke. Infants are twice as likely to die from SIDS if their mothers stop smoking during pregnancy and then resume following birth, in comparison to those who do not resume smoking.
- Secondhand smoke affects children their entire lives. As adults, they may face an increased risk of developing lung cancer if they grow up in a home with a smoker.
- In January 1993, environmental tobacco smoke joined asbestos, benzene, and vinyl chloride as a Group A" carcinogen. These are carcinogens *for which no safe level of exposure has been established.*
- ETS contains 43 chemicals that have been determined to be carcinogenic, many of which are treated as hazardous when emitted by toxic waste dumps and chemical plants.
- An estimated 3,000 lung cancer deaths in healthy non-smokers are caused each year by ETS.

In recent months, several fast food restaurants, most notably McDonald's, have gone smoke-free. The concentration of secondhand smoke in these establishments, places where our children eat, play, and often work, is alarming:

- Exposure to secondhand smoke in restaurants that allow smoking is 1½ to 2 times greater than in other workplace settings that allow smoking, such as offices.
- Exposure to secondhand smoke in restaurants is 1½ times greater than in homes where at least one parent smokes.
- Restaurant workers have a 50 to 90 percent increase in lung cancer risk due to their exposure to secondhand smoke. They are 1½ to 2 times as likely to develop lung cancer than if they worked in smoke-free restaurants.

I maintain that our first order of business is to share these disturbing facts with every parent in this country. No parent would willingly expose their child to any danger—and secondhand smoke is undeniably a danger.

My second order of business is to state for the record that these risks were amply documented in hundreds of research studies reflected in the 1986 Surgeon General's Report on Tobacco, *The Health Consequences of Involuntary Smoking*. This report represented the work of more than 60 distinguished physicians and scientists, both in this country and abroad. After careful examination of the existing evidence, these scientists reached the following overall conclusions:

- Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers.
- Simple separation of smokers and non-smokers within the same air space does not eliminate exposure of non-smokers to environmental tobacco smoke.
- The children of parents who smoke have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increases in lung function as the lung matures.

The foreword to the report concluded that:

> ". . . . it is clear that actions to protect nonsmokers from ETS exposure not only are warranted but are essential to protect public health."

Today we stand with those findings and the even stronger findings of the EPA that clearly document the deadly health consequences of environmental tobacco smoke.

At Chairman Waxman's hearing, I joined Administrator Browner and all five former Surgeons General in supporting H.R. 3434, the Smokefree Environment Act of 1993. Today I am pleased to add my support to S. 1680, the Smokefree Environment Act of 1993, and we look forward to working with the Subcommittee over specific concerns as the bill is debated. I look forward to working with the Senate to protect the public from this enormous and unnecessary health risk, particularly our children.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

The Surgeon General of the
Public Health Service
Washington DC 20201

JUN 9 1994

Senator Joseph Lieberman
Chairman
U.S. Senate Committee on Environment and Public Works
Subcommittee on Clean Air and Nuclear Regulations
316 Hart Senate Building
Washington, D.C. 20510

Dear Senator Lieberman:

On May 11, I testified before the Senate Committee on Environment and Public Works, Subcommittee on Clean Air and Nuclear Regulations, during its hearing on S. 1680, the Senate companion bill to H.R. 3434, the Smokefree Environment Act. I am pleased to have had the opportunity to testify for the Administration in support of this proposed legislation.

At this same hearing, the Congressional Research Service (CRS) presented testimony which questioned the validity of the Environmental Protection Agency's (EPA) risk assessment on the health effects of exposure to environmental tobacco smoke (ETS). I would like to submit for the record an analysis by the U.S. Centers for Disease Control and Prevention (CDC) of the CRS report, "Cigarette Taxes to Fund Health Care Reform: An Economic Analysis," upon which that testimony was based. Because of the weight of scientific evidence regarding the health effects of exposure to ETS, I feel it is important to include this in the record of the hearing.

We are working expeditiously on other specific information you requested for the hearing record, and we will provide it to you as soon as possible.

Thank you for this opportunity to contribute to Congressional deliberations on this important public health issue.

Sincerely,

M. Joycelyn Elders

M. Joycelyn Elders, M.D.
Surgeon General

Enclosure

STATEMENT BY CENTERS FOR DISEASE CONTROL AND PREVENTION

In its report, "Cigarette Taxes to Fund Health Care Reform: An Economic Analysis," the Congressional Research Service (CRS), assesses the health risks of environmental tobacco smoke (ETS) and disputes well-documented scientific evidence that exposure to ETS is a cause of disease. The CRS report concludes that the link between passive smoking and disease is uncertain, and that epidemiologic studies suggesting a link are scientifically flawed. In reaching these conclusions, the CRS report regrettably has discounted the fundamental principles and scientific rigor of epidemiology, as well as the immense body of research on ETS exposure.

It would not be appropriate to consider the CRS report a review or analysis of the evidence relating to the health effects of ETS exposure. Hundreds of studies, including the 1986 Report of the Surgeon General, *The Health Consequences of Involuntary Smoking*, document the relationship between ETS and health outcomes. The CRS report directly cites only two studies,' and based on these two references, reaches conclusions unsupported by the preponderance of scientific evidence.

In testimony before the United States Senate, the authors acknowledge limitations in their qualification to conduct a valid epidemiologic analysis. They note that, as economists, their area of expertise is "economic analysis and the associated areas of statistical inference and quantification of effects for purposes of cost-benefit analysis and related economic policies," rather than the "physiological and biological transmission mechanisms of disease causing agents."

Most importantly, the CRS report challenges the EPA risk assessment on lung cancer and ETS exposure. The EPA report was written and reviewed by many reputable scientists trained in the causation and prevention of disease. The Department of Health and Human Services fully supports this report as an accurate assessment of the health risks of ETS exposure. Accepting conclusions on issues of disease causation by any but the consensus of medical and epidemiologic scientists would be a serious mistake.

The following are the most important areas of public health concern in the CRS report on the health risks of exposure to ETS:

1. On page 45, the report raises questions about whether there is a dose-response relationship between tobacco smoke exposure and adverse health effects over the wide range of ETS levels to which nonsmokers are exposed. The epidemiologic data in this regard, however, are clear. The weight of the evidence shows that the risk of lung cancer rises as ETS exposure levels increase.

2. On page 45, the report suggests that there may be a threshold level below which there is no biological damage from ETS exposure. The existence of a threshold for tobacco smoke in lung cancer is theoretically possible, but there are no empirical data to support the threshold concept and most scientists argue against a threshold for any carcinogen. Indeed, the data that do exist clearly favor the nonthreshold hypothesis. Virtually every one of the thousands of studies evaluating lung cancer among smokers shows that risks increase in proportion to level of smoking, with demonstrable increases in risk even among the very lightest smokers.

3. On page 45, the report suggests that the relationship between tobacco smoke exposure and health effects at the level of passive smoke exposure is such that the effects would be minor. The CRS report refers to the 1989 Surgeon General's report citation (page 44) of a cohort study of lung cancer and smoking among about 34,000 British physicians. This study estimated that risk of lung cancer rose in proportion to the square of the number of cigarettes smoked per day. The CRS states that this implies that the relation is "strongly nonlinear." This statement is questionable, since the departure from linearity with the quadratic model may not be great. More importantly, the CRS report disregards data presented on page 45 of the same Surgeon General's report. There, a graph is presented showing a clearly linear relation between the number of cigarettes smoked per day and lung cancer risk. The data on page 45 derive from a much larger cohort study of nearly 250,000 American veterans.

4. On pages 47 and 48, the report expresses concerns about the use of a one-tailed test of significance (approximately equivalent to using a 90 percent confidence interval to test the chance that a relative risk differs from 1.0), even though it offers no plausible reason to believe that exposure to ETS may decrease lung cancer risk. Although 95 percent confidence limits are commonly used, 90 percent confidence intervals are often used in health studies, and are in fact standard in epidemiologic studies of agents such as radiation, which like tobacco, is a strong lung carcinogen. In putting a large emphasis on this rather minor part of the analysis, the report ignores the importance of other factors used by epidemiologists in causal inference, such as consistency of association, strength of association, temporality of the association, dose-response relationship and biologic plausibility.

5. On page 48, the report suggests that recall bias may invalidate the conclusion of an adverse health effect of ETS exposure. This ignores the fact that there is a consistent association between ETS exposure and disease even in four cohort studies, in which recall bias cannot occur, because exposure is ascertained before disease has occurred.

6. On page 48, the report suggests that confounding factors may explain the observed association between ETS exposure and lung cancer. However, it does not suggest a single factor that could plausibly explain the association. Specifically, it does not point out any factor that is a strong independent risk factor for lung cancer that is also strongly related to ETS exposure. Moreover, the consistency of results across a wide variety of study designs and populations argues against confounding as an explanation of the consistent study findings. A wealth of data on cigarette smoking indicates that it is an independent cause of several chronic diseases.

7. In their testimony, she authors of the CRS report suggest that the presence of a consistent dose-response relationship in the epidemiologic studies should not have increased confidence in the conclusion of a causal relationship between ETS and lung cancer. This statement is in direct conflict with one of the most basic principles of epidemiology.

8. In their testimony, the authors suggest that the findings of two recent studies, published too late to be included in the EPA review, cast doubt on the relationship between ETS and lung cancer. On the contrary, in combination these studies are entirely consistent with the body of epidemiologic evidence on the issue, and they add additional support for the conclusion that ETS increases lung cancer risk. The authors of the CRS report ignored the published conclusions of both of these studies.

Specifically, in the Brownson study, the authors found an elevated lung cancer risk for adults with more than 40 pack-years of exposure to ETS from household members, and concluded that "exposure to high levels of environmental tobacco smoke in adulthood increases the risk of lung cancer in nonsmokers."

In the Stockwell study, the authors found that the risk of lung cancer more than doubled for women with more than 40 pack-years of household ETS exposure and conclude that "long-term exposure to environmental tobacco smoke increases the risk of lung cancer in women who have never smoked."

9. The authors attempt to determine the risk of passive smoking by extrapolating from urinary cotinine levels in active compared to passive smokers. They conclude that the average exposure is 0.1 cigarette equivalents per day. However, using this same approach, Guerin *et al.* have shown that 0.1 cigarette equivalents of exposure to nicotine in inhaled air implies exposure to 60 cigarette equivalents of pyridine and 56 cigarette equivalents of ammonia. The concentrations of many of the carcinogenic components of tobacco smoke are much higher in sidestream than in mainstream smoke. But it is exposure to these components, and not to nicotine, that is likely to determine the lung cancer risk among exposed nonsmokers.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

The Surgeon General of the
Public Health Service
Washington DC 20201

JUN 20 1994

Senator Joseph Lieberman
Chairman
U.S. Senate Committee on Environment and Public Works
Subcommittee on Clean Air and Nuclear Regulations
316 Hart Senate Building
Washington, D.C. 20510

Dear Senator Lieberman:

This is to respond to questions from Senator Faircloth, as forwarded to me by your office on May 23, 1994.

Senator Faircloth asked several questions to clarify my qualifications to assess the health risks of environmental tobacco smoke (ETS). In addition to being trained as a pediatrician, and having practiced clinical medicine, as U.S. Surgeon General I supervise the United States Public Health Service, consisting of many of this country's finest epidemiologists. My statements on ETS are based on an extensive, epidemiologic and scientific review of the evidence. Enclosed is my resume which shows the clinical experience and training I have had. I hope this answers the Senator's questions about my background.

As to the questions raised relating to environmental tobacco smoke (ETS), asthma, and restaurant workers, I would offer the following:

(1) Senator Faircloth inquired as to significant differences between mainstream and sidestream smoke that have an effect on health.

There are important differences between mainstream and sidestream tobacco smoke that explain why exposure to environmental tobacco smoke (ETS) is so harmful. Most importantly, the concentrations of many of the toxic and carcinogenic components of tobacco smoke are much higher in sidestream than mainstream smoke, especially for many carcinogens. For example, the concentration in sidestream smoke is 5-10 times higher for benzene, up to 50 times higher for formaldehyde, 19 times higher for o-toluidine, 20-100 times higher for N-nitrosodimethylamine, 30 times higher for 2-napthylamine, and 31 times higher for 4-aminobiphenyl. The vapor phase alone in sidestream smoke contains carbon monoxide, carbonyl sulfide, benzene, formaldehyde, 3-vinylpyridine, hydrogen cyanide, hydrazine, nitrogen oxides, N-nitrosodemethylamine and N-nitrosopyrrolidine. Moreover, biological measurements in ETS-exposed individuals have documented elevated levels of plasma and urine cotinine and plasma thiocyanate, increased urine mutagenicity, and elevated levels of 3-aminobiphenyl, a carcinogenic hemoglobin adduct. Thus, not only are passive smokers exposed to high levels of toxic chemicals, they exhibit biological changes from their exposure.

(2) Senator Faircloth asked about clinical diagnoses of asthma in children and the relationship between childhood asthma and exposure to ETS.

Clinicians often determine the cause of a child's asthma or respiratory illness from the history and clinical examination. Because ETS is an acknowledged, common contributing factor for asthma exacerbations, most clinicians recommend that asthmatic children avoid exposure to ETS.

Scientific evidence demonstrates that children exposed to ETS experience real and measurable effects from their exposure. Besides exacerbating asthma, ETS is believed to cause up to 26,000 new cases of asthma among children each year. Because children do not control their breathing environments, the threat of ETS to children is particularly insidious.

INNER CITY CHILDREN AND ASTHMA

Living conditions, environment, and access to medical care are important indicators for health, including the health of children with asthma. However, studies demonstrate that when asthmatic children are exposured to ETS their condition is exacerbated and that 26,000 new cases of asthma in children may be caused by exposure to ETS.

Epidemiologists are trained to separate out the most likely risk factors from the many which may cause disease. For example, smoking, high cholesterol, high blood pressure, diabetes and obesity have all been identified as risk factors for heart disease. The presence of multiple risk factors for a disease does not preclude epidemiologists from identifying each as an independent risk factor. Epidemiologists base conclusions of what constitutes a risk factor on data that compare rates of disease in those exposed and not exposed to that risk factor.

Relatedly, while parental smoking may be associated with other poor health habits, these other factors do not sufficiently explain the strong and consistent association between ETS exposure and the development of asthma in children. The most plausible explanation at this time is that ETS is, in fact, an independent risk factor for the development of asthma.

(4) Senator Faircloth requested clarification on health risk assessments for restaurant workers exposed to ETS.

A review published in the Journal of the American Medical Association (July 28, 1992, Volume 270, Number 4, Pages 490-493) reported that levels of ETS in restaurants are 1.5 to 2 times higher than in typical workplaces and that levels of ETS in bars are 4 to 6 times higher. The article reviewed six published studies comparing the risk of lung cancer in restaurant workers to the lung cancer risk among the general population. Based on this review, the article concluded that restaurant workers are 1.5 to 2 times more likely to develop lung cancer than they would be if restaurants were smokefree.

These epidemiologic studies did not measure workers' exposure to ETS. However, there are no other apparent exposures that could explain the consistent finding of an elevated lung cancer risk among restaurant workers.

The Centers for Disease Control and Prevention's Office on Smoking and Health has reviewed the published research on ETS levels in bars, restaurants, offices, homes, and other environments. The levels of ETS in restaurants and bars were 1.5 to 6 times higher than in typical offices. Since the Occupational Safety and Health Administration estimates that ETS exposure in the workplace causes between 140 and 700 cancer deaths per year, the finding that ETS levels in bars and restaurants exceed the levels in typical workplaces is alarming. It suggests that ETS exposure is a significant health hazard for food service workers. The epidemiologic evidence strongly supports this conclusion.

Again, thank you for the opportunity to testify on this important public health issue and to respond to Senator Faircloth's questions.

Sincerely,

M Joycelyn Elders

M. Joycelyn Elders, M.D.
Surgeon General

STATEMENT DR. CHRIS COGGINS, R.J. REYNOLDS TOBACCO COMPANY, ON BEHALF OF THE TOBACCO INSTITUTE

INTRODUCTION

The Tobacco Institute welcomes this opportunity to address the Environmental Protection Agency's 1992 report ("the EPA Report") on environmental tobacco smoke (ETS). Viewed objectively, the EPA Report and its conclusion do not provide a sound scientific basis for public policy concerning ETS.

The EPA Report classified ETS as a Group A carcinogen under the EPA's own classification scheme. EPA based this classification primarily on (1) epidemiologic studies on ETS and (2) the purported similarities between mainstream cigarette smoke and ETS. Neither (alone or in combination) provides a scientific foundation for EPA's conclusion.

To arrive at its classification of ETS as a Group A carcinogen, EPA deviated from accepted principles of chemistry, epidemiology and toxicology, as well as its own guidelines for conducting cancer risk assessments. EPA manipulated and "cherry-picked" scientific data, ignored contrary studies, and employed models, assumptions, and methodologies not accepted by the scientific community (including EPA in other contexts).

I. Epidemiology and the 30 World-Wide Studies

Epidemiology is the study of the occurrence of disease in human populations. Investigators observe patterns of disease occurrence and attempt to statistically correlate disease with potential causes of disease. Specifically, epidemiologists compare the incidence or rate of disease in a group exposed to the factor being studied ("cases") to the incidence or rate in a second group unexposed to the factor being studied ("controls"). The results of the studies are reported as statistical correlations or associations which are commonly expressed as relative risks. A relative risk is the ratio of the disease incidence rate in the exposed group to the incidence rate in the unexposed group. A relative risk of 1.0 indicates that the observed disease incidence rate in the exposed group is the same as that in the unexposed group. In other words, there is no increased risk observed in the exposed group. A relative risk above 1.0 indicates that the disease incidence rate is greater in the exposed group (i.e., an increased risk is observed), while a relative risk less than 1.0 indicates that the disease incidence rate is smaller in the exposed group (a "protective" effect).

EPA has adopted certain criteria by which it evaluates epidemiologic data. These criteria are set forth in EPA's cancer risk assessment guidelines, "Guidelines for Carcinogen Risk Assessment," 51 Fed. Reg. 33992[1] (Sept. 24, 1986) (the "Risk Assessment Guidelines"). The Risk Assessment Guidelines require that, before a conclusion regarding whether an exposure causes a disease (a causal inference) can be based upon epidemiologic data, three criteria must be met:

(i) the apparent statistical association must be unlikely to be produced by chance;

(ii) the possibility of confounding (i.e. the role of other actual or potential factors in the apparent association) must have been considered and ruled out as an explanation for the association; and

(iii) there must be no identified bias that could explain the apparent association.

A. The Role of Chance Cannot Be Ruled Out as an Explanation for Any Statistical Association

The test of statistical significance is crucial to the scientific analysis of epidemiologic data. Without this test, cause and effect conclusions can be erroneously attributed to associations occurring by chance alone, simply due to random sampling variation. Because chance occurrences can never be completely excluded from a study, the likelihood or probability that an observed association could be due to chance is expressed through the use of tests for statistical significance.

Statistical significance tests are often expressed in terms of a confidence interval, which is a numerical range for the point estimate (which is the specific relative risk value). A confidence interval calculated with a 95 percent confidence level, for example, is referred to as a 95 percent confidence interval: here we would be 95 percent certain that the point estimate for the relative risk lies within the given upper and lower limits. Stated differently, with a 95 percent confidence level, an epidemiologist is prepared to accept a one in 20 chance of being wrong in predicting that the relative risk truly lies within this range.

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[1] 51 Fed. Reg. 33999. These guidelines have recently been endorsed in principle by the National Research Council. "Science and Judgment in Risk Assessment", National Academy Press, Washington, DC, 1994. In addition, EPA states in the EPA Report that epidemiologic data must also be assessed against other criteria including: the consistency of the data, the strength or magnitude of the statistical association, and whether the data exhibit a dose-response gradient. EPA failed to fulfill its obligations under its own standards.

An apparent association or relative risk is said to be not statistically significant at the 95 percent confidence level unless the *entire range* for that risk is above (or below) 1.0. By generally accepted scientific convention, at least a 95 percent confidence level is required in epidemiologic studies to conclude that an association is statistically significant.

In its ETS assessment, EPA reviewed 30 published epidemiologic studies. The studies primarily address whether a nonsmoking woman's risk of lung cancer may be statistically correlated with whether or not her spouse smokes. The studies do not measure actual ETS exposure. Instead, they rely simply on questionnaire responses as to whether a woman's spouse smokes. These responses provide the only information on ETS exposure.

A brief review of these studies provides information that is contrary to the EPA's conclusion but that is too often overlooked or simply ignored. Of the 30 published studies EPA relied upon, 11 were conducted in the United States. As originally reported, *none* of the U.S. studies reports an overall risk estimate for lung cancer that is statistically significant. Of the remaining 19 studies (conducted outside the United States), 13 found no overall statistically significant association between spousal smoking and lung cancer. In total therefore, 24 of the 30 studies reviewed by EPA—80 percent—as originally reported in the published literature do not support the EPA's conclusion. One study even shows a statistically significant protective effect.

In the face of these results, EPA "reanalyzed" the 30 epidemiologic studies. Specifically, EPA lowered the threshold for achieving statistical significance by lowering the standard 95 percent confidence level (employed in 27 of the 30 studies) to an unorthodox 90 percent confidence level. In altering the original analyses of the authors of the studies, EPA doubled the possibility that any statistically significant association is simply a random and meaningless event. In other words, with 90 percent confidence limits, EPA accepts a one in ten chance that the relative risk is not in fact within the confidence interval. EPA's use of the lower 90 percent confidence level in the final EPA Report stands in stark contrast to (i) its use of the generally accepted 95 percent level in the 1990 draft of the ETS Risk Assessment, (ii) the use of the 95 percent level in 27 of 30 original reports themselves, and (iii) EPA's routine use of studies employing the 95 percent level in other carcinogen risk assessments.

Even after reanalyzing the studies using the lower confidence level, EPA failed to obtain a statistically significant overall association from over two-thirds of the world-wide studies. Of the 11 U.S. studies, only one yielded a statistically significant association after reanalysis.

Skepticism about and criticism of EPA's arbitrary manipulation of the statistical significance standard did not begin with the tobacco industry. And, the tobacco industry does not stand alone in raising serious questions about the propriety of EPA's approach. In a report released just 2 months ago, the Congressional Research Service of the United States Congress questioned EPA's approach:

> One thing EPA did in its assessment is change the standard for statistical significance from the usual standard, and the one generally used in the original studies. Admittedly, it is unusual to return to a study after the fact, lower the required significance level, and declare its results to be supportive rather than unsupportive of the effect one's theory suggests should be present.[2]

The large number of studies which report no overall statistically significant association between ETS and lung cancer overwhelm the few studies that EPA claims demonstrate an association and suggest that those few results may simply be the result of chance. When this evidence is coupled with EPA's choice of a confidence level which doubles the risk that an association due to chance will be labeled statistically significant, chance becomes the likely explanation for any statistical association claimed by EPA between ETS and lung cancer.

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[2] Congressional Research Service, "Cigarette Taxes to Fund Health-Care Reform: An Economic Analysis", CRS Report For Congress, at 47 (March 8, 1994) (hereafter "CRS Report").

B. Confounding Cannot Be Ruled Out as an Explanation for the Reported Association Between Spousal Smoking and Lung Cancer Risk

Confounding of data exists when an association between a disease and an exposure to one agent can be explained, in whole or in part, by an exposure to a second agent that is associated with both (a) the disease and (b) the first exposure. Potential confounding factors undermine the reliability of epidemiologic data because of the difficulty in disentangling the influence of one factor from the influence of another.

According to its own protocol, EPA may not infer causation unless "[t]he possibility of confounding has been considered and *ruled out* as explaining the association." 51 Fed. Reg. 33999 (emphasis added). Here again, EPA violated accepted scientific standards and its own guidelines.

The scientific literature identifies the following factors, among others, as potential confounders: diet, personal medical history, family health history, lifestyle choices, occupational factors, and environmental factors.

In its ETS assessment, EPA acknowledged the existence of some potential confounding factors but ignored many others. EPA stated that it had ruled out confounding—largely because it claimed to be unable to identify any single confounding factor that in itself would explain the apparent association between ETS and lung cancer which appeared in EPA's analysis. This approach does not come close to considering adequately the possible role of confounding factors. And, it certainly does not "rule out" the possibility of confounding.

Studies published since release of the EPA Report (as well as studies published prior to its release) confirm (1) the likelihood that the spousal smoking studies are confounded, and (2) the importance of resolving the confounding issue *before* drawing conclusions.

In 1993, Thompson and Warburton reported a number of lifestyle similarities between individuals living in smoking households:

> [I]ndividuals living in smoking households consumed fats more frequently, drank more alcohol and were less likely to eat root vegetables and cereal [than individuals living in nonsmoking households]. In addition, those in smoking households seem to show higher rates of depression and insomnia, which are also negative health indicators.[3]

These results suggest that caution should be exercised when interpreting the disease patterns of non-smokers in smoking households, because all of the above differences have been cited as risk factors for cancer.[4]

In 1994, Cress *et al.* found significant lifestyle and personal differences between women living in a smoking household and women not exposed to ETS:

> [ETS exposed] women were younger, less educated and slightly heavier than nonexposed women. They were more likely to be divorced or separated, to have had first intercourse at or before age 16, and to have had three or more live births. Women exposed to passive exposure were more likely to have consumed two or more cups of coffee, two or more glasses of beer or to have smoked marijuana in the past 24 years.[5]

They noted that "studies that have investigated the association between passive exposure and increased risk of disease have had *inconclusive results* and have raised questions about whether women exposed to passive smoke differ from those not exposed."[6] They concluded that—

> Women exposed to passive smoke differed from those not exposed on several factors that should be considered in future studies that seek to investigate . . . disease.[7]

This point must not be ignored in public policy discussions about ETS, because the ramifications are profound:

> If wives of smokers share in poor health habits or other factors that could contribute to illness and that are not or cannot be controlled for, statistical as-

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[3] Thompson, D.H., Warburton, D.M., "Dietary and Mental Health Differences Between Never-Smokers Living in Smoking and Non-Smoking Households," J. Smoking-Related Dis. 1993: 4(3): 203–211. They cautioned:

[4] *Id.*

[5] Cress, *et al.*, "Characteristics of Women Nonsmokers Exposed to Passive Smoke, Preventive Medicine 23, 40–47 (1994).

[6] *Id.*

[7] *Id.*

sociations found between disease and passive smoking could be incidental or misleading.[8]

C. Various Sources of Bias Can Explain Any Association

Bias in statistics refers to any trend in the design, collection, analysis, interpretation or publication of statistical data that causes or may tend to cause a systematic distortion of the true nature of the relationship studied.

Bias must be excluded as an explanation for an observed association before it can be concluded that a statistically significant association exists. Various sources of bias, including publication bias and respondent bias, could explain any association claimed by EPA between ETS and lung cancer.

EPA recognized only one source of bias in its Risk Assessment—the tendency of smokers to misrepresent themselves as nonsmokers ("smoking status misclassification bias")—and chose to adjust for it by using an unpublished scientific model that contains numerous mathematical and conceptual inconsistencies, including incorrect assumptions. EPA used a misclassification rate considerably lower than other estimates. If EPA had used representative data, EPA's own analysis would not have resulted in a statistically significant association between ETS and lung cancer.

D. The Statistical Association Claimed by EPA Is Weak

Strength refers to the magnitude of an apparent association. Associations of less than 3.0 are generally considered in the scientific community and by EPA to be weak and equivocal. Associations under 2.0 are considered to be extremely weak and are far more likely to be an artifact produced by chance, bias or confounding than are stronger associations. The weaker an association, the less reliable it is for evaluating a potential causal relationship. EPA admits as much in stating in its Risk Assessment Guidelines that "epidemiologic studies are inherently capable of detecting only *comparatively large* increases in risk."[9]

Of the 30 epidemiological studies analyzed by EPA in connection with its classification of ETS as a Group A carcinogen, 80 percent did not report an overall statistically significant association of any magnitude between ETS and lung cancer. Even ignoring statistical significance, all of the studies reported overall relative risks under 3.0, and 21 reported overall relative risks under 2.0. Six of those 21 even reported associations below 1.0. Even when the 11 U.S. studies were pooled by EPA, the adjusted relative risk estimate it constructed was only 1.19.

Dr. Morton Lippmann, chairman of the committee of the EPA's Science Advisory Board ("SAB") which reviewed the EPA Report, acknowledged the weakness of the association found by EPA when he noted to reporters at a press conference called to publicize the draft that the risk of ETS was "probably much less than you took to get here through Washington traffic."

Because any statistical associations between ETS and lung cancer relied upon by EPA are so weak, it is very likely that they are produced by chance, bias, or confounding, or combinations thereof, rather than reflecting a true causal association.

II. EPA's Meta-Analysis Is Flawed

Analysis of the individual epidemiologic studies could not support a Group A classification; therefore, EPA combined or pooled select portions of the data from the epidemiological studies using a controversial technique known as meta-analysis. This exercise not only did nothing to eliminate the bias, confounding, and methodologic flaws that are prevalent in the individual epidemiologic studies, it introduced new and different errors and flaws into the analysis.

First, relying solely on data regarding U.S. women and employing its unorthodox confidence level, EPA calculated a pooled relative risk estimate of 1.19, which is *extremely* weak. If EPA had consistently used its own data selection criteria and the accepted 95 percent confidence level, its meta-analysis would have yielded no statistically significant association at all.

Second, EPA's meta-analysis did not even comport with guidelines that apply to meta-analysis. Practitioners in this area agree that meta-analyses can have utility only when (a) the studies that are to be combined are similarly designed and conducted, and (b) like data are pooled with like data. The studies EPA reviewed do not begin to meet these criteria (as well as others that have been developed for meta-analyses). For example, some studies are "case control" or retrospective (examining the exposure *histories*) studies, and others are "cohort" or prospective (following groups *forward* in time) studies; some studies classify ex-smokers as smokers and others classify them as non-smokers; some studies attempt to control for selected confounders and others do not; some studies exclude one tumor type and others use *only* that tumor type. The studies are too dissimilar in many respects to be pooled in a way to draw any conclusions.

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[8] CRS Report at 48. Despite EPA's (and others') claims to the contrary, the possibility of confounding cannot be ruled out as the explanation for any reported association between ETS and lung cancer.

[9] 51 Fed. Reg. 33996 (emphasis added).

Third, EPA manipulated, ignored and cherry-picked data for inclusion in the meta-analysis. For example: EPA completely ignored two large studies published in the United States (Brownson and Stockwell)[10] although these studies were brought to EPA's attention prior to its release of the final EPA Report. Brownson is the largest study published on spousal smoking status and lung cancer and was sponsored by the National Cancer Institute. It reports no increased risk for overall exposure to spousal smoking—notwithstanding an often quoted excerpt from the *abstract* that is plainly at odds with the actual data from the study. EPA violated its own criteria for determining what data to select with respect to one study (Janerich)[11]. Specifically, EPA used unadjusted risk estimates from household exposure from Janerich while it used adjusted risk estimates from spousal exposure from all other studies from which adjusted risk estimates could be derived.

Fourth (and as described above), EPA failed to adjust adequately for smoking status misclassification bias, which is known to inflate the apparent association observed in studies of spousal smoking and lung cancer. Although EPA acknowledged this one source of bias and purported to adjust for it, EPA used a method of adjustment based on unrepresentative data instead of more representative data. EPA's use of these unrepresentative data resulted in an extremely low and unrealistic rate of adjustment that is not representative of the U.S. population for this crucial variable. More recent, reliable, and realistic data demonstrate that representative rates of misclassification are between 4 and 6 times larger than the rate used by EPA.

In summary, the weak apparent association produced by EPA's meta-analysis results from either failures to account for bias and confounding factors or from outcome-determinative choices EPA made when selecting methodology, data and studies to employ. When even small changes or corrections in the assumptions or methods employed by EPA are made, the results of the meta-analysis change from being statistically significant to being statistically non-significant. A few examples demonstrate that the EPA's conclusions are built on a weak foundation indeed:

- EPA could not have achieved its alleged statistically significant association between ETS and lung cancer without changing the confidence level.
- If EPA had used correct data from one study (the Janerich study) and employed the standard 95 percent confidence level, its meta-analysis would have resulted in *no statistically significant association.*
- Evaluating the 11 U.S. studies reviewed by EPA plus the Brownson and Stockwell studies demonstrates that there is a reduction with time in the overall variability, as more confounders are identified and are corrected for. This is called the "funnel effect." The more recent studies (with little variability in the data) in general do not show increases in risk. The funnel effect for the ETS studies also shows a clearly decreasing trend for the relative risks with time.
- If EPA had included data from the Stockwell and Brownson studies in its meta-analysis, there would be *no statistically significant association*—even accepting EPA's use of the lower confidence level.
- If EPA had used a realistic and supportable smoker misclassification rate of 5 percent, *no statistically significant association* would have resulted.

III. A Dose Relationship Has Not Been Shown

A dose-response relationship means that as the extent of exposure, and hence dose, increases, the observed incidence of disease also increases.

The Risk Assessment Guidelines note the importance of finding a dose-response relationship when trying to determine if an observed association is causal. 51 Fed. Reg. 33999. EPA attempted to satisfy this criterion by employing another unorthodox approach: the substitution of a test for "trend" for a true dose-response test. A trend test does not measure dose-response and is not an accepted substitute for a dose-response analysis.

None of the 30 epidemiologic studies relied upon by EPA shows a statistically significant dose-response relationship. Several studies actually show a reverse dose-response, *i.e.*, higher reported levels of spousal smoking are associated with an apparent *decreased* risk of lung cancer. One study reported a reverse dose-response that was statistically significant.

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[10] Brownson, R.C., M.C.R. Alavanja, E.T. Hock, and T.S. Loy, "Passive smoking and lung cancer in nonsmoking women," American Journal of Public Health 82, 1525–1530 (1992); Stockwell, H.G., A.L. Goldman, *et al.*, "Environmental tobacco smoke and lung cancer in nonsmoking women," Journal of the National Cancer Institute 84, 1417–1421 (1992).

[11] Janerich, D.T., W.D. Thompson, *et al.*, "Lung cancer and exposure to tobacco smoke in the household," New England Journal of Medicine 323, 632–636 (1990).

IV. ETS Is Very Different From Mainstream Smoke

EPA also attempts to support its decision to classify ETS as a Group A carcinogen on an independent ground: review of selected data relating to mainstream smoke (the smoke inhaled by a smoker) (MS)—a proxy substance. Specifically, EPA claimed that similarities between ETS and MS coupled with the assumption that *any* exposure to MS poses a lung cancer risk, justified a Group A classification for ETS. Common-sense and basic principles of chemistry and toxicology belie this conclusion.

First, ETS is not the equivalent of MS. ETS is a highly dilute, complex and dynamic mixture of sidestream smoke ("SS"), exhaled MS and some diffused tobacco smoke emanating from the tobacco rod. Very few of the chemical constituents identified in MS have been identified in ETS in ambient air. Indeed, EPA must resort to inferring that ETS contains the "same carcinogens" as mainstream smoke because, as a practical matter, the presence of most components of ETS can only be postulated since they are beyond the detection capability of modern analytical techniques. The general physical and chemical properties of the two smokes, including pH, constituent-phase distribution, and other physicochemical traits, differ significantly. For example, ETS is perhaps as much as 100,000 times more dilute than mainstream smoke, with much lower humidity and extremely low concentrations of volatiles.

ETS is not just a quantitative variant of MS (as some claim). As recognized by the public health community, the demonstrable differences between ETS and MS preclude any rational analysis of ETS based on data relating to mainstream smoke. The Surgeon General concluded in 1986 that knowledge of MS chemical composition is of limited assistance in evaluating ETS: "Comparison of the relative concentrations of various components of SS and MS smoke provides limited insights concerning the toxicological potential of ETS in comparison with active smoking."[12]

Similarly, when requested in 1986 by the EPA and others to review ETS and health studies, the National Research Council concluded that data on MS do not provide a basis for predicting ETS exposure effects: "Because the physicochemical nature of ETS, MS, and SS differ, the extrapolation of health effects from studies of MS or of active smokers to nonsmokers exposed to ETS may not be appropriate. . . ."[13]

EPA itself concedes and relies upon the substantial differences between MS and ETS elsewhere in the EPA Report. For example, in Chapter 6, which purports to calculate a population risk of lung cancer from passive smoking, EPA states:

> This assumption [comparing MS and ETS to calculate lung cancer risks] may not be tenable, however, as MS and SS differ in the relative composition of carcinogens and other components identified in tobacco smoke and in their physicochemical properties in general. . . .

Second, even if ETS and MS were nearly identical, the immense quantitative differences between ETS exposure and cigarette smoking would independently preclude reliance on proxy review of MS. There is strong evidence *against* EPA's assumption that any exposure to ETS, no matter how small, poses a cancer risk. Certain ETS constituents such as particulate matter and ambient nicotine can be measured in the ambient air. Based on those data, scientists have consistently estimated that an ETS-exposed nonsmoker is exposed to the range of one to five cigarette equivalents per *year*. According to a recent published review, data from several epidemiologic studies on active smoking suggest that smoking four to five cigarettes per *day* is not likely to be associated with a statistically significant increased risk of lung cancer. Differences in retention can further expand these dosimetric differences. For example, it is estimated that the average ETS exposed person appears to retain between 10,000 and 100,000 times less smoke particulate matter than a cigarette smoker. EPA's assumption that no threshold exists for ETS exposure relies solely on active smoking studies which have as their lowest exposure range 1–7, 1–9, 1–14 or <20 cigarettes smoked per day. All of these ranges are far in excess of the highest dose conceivably attributable to ETS.

One of the basic tenets of toxicology is that "the dose makes the poison." All things can be poisons, depending on the dose. Any real-world estimates of ETS concentrations represent such trivial doses that it is scientifically implausible that they could result in meaningful toxicological activity.

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[12] 1986 Surgeon General's Report at 24.

[13] National Research Council, Environmental Smoke: Measuring Exposures and Assessing Health Effects, National Academy Press 1986 at 7–8.

Moreover, in the absence of a clear congressional mandate to the contrary, EPA is required to make a finding that a risk is *significant* before taking such action as classifying ETS as a Group A carcinogen. EPA's "no-threshold" assumption is an insufficient basis upon which to make such a finding. Indeed, if the presence in any quantity of a chemical reported in mainstream smoke were a sufficient basis for declaring a substance to be a Group A carcinogen, EPA could similarly classify outdoor air, hamburgers, milk, peanut butter, and a host of other substances as Group A carcinogens.

V. Animal Studies Fail To Show any Meaningful Toxicologic Change

The EPA Report pays little attention to inhalation studies with smoke. The EPA preferred to concentrate on statistical studies than to do a study with animals, although the latter studies allow most of the variables to be controlled. Although there are some data in the EPA Report on inhalation studies (with smoke), on intrapulmonary implantation studies (using condensate) and on mouse skin painting studies (also using condensate), none of these studies used ETS or even a reasonable surrogate.

EPA refused to consider a series of rat inhalation studies using aged and diluted sidestream smoke (as a surrogate for ETS). Animals were exposed for six hours per day, 5 days per week, for 13 weeks. The selected concentrations included a reasonable estimate of "real world" exposure, along with ten and one hundred-fold exaggerations. No toxicological or pathological changes were observed in the animals, except for a small, reversible and non-progressive change seen only in the high exposure group. EPA refused to consider these results, even though the study was submitted for peer review and accepted for publication. That study has now been published in scientific peer review journals.Inhalation Toxicology 5 (1993), 77–96; Fundamental & Applied Toxicology 20 (1993), 393–401.

CONCLUSION

Viewed objectively, the EPA's conclusions about ETS are based on weak and contradictory evidence and selective arguments. The EPA's approach, much less its conclusions, would not withstand real scientific peer review. The EPA Report simply does not provide a sound basis for public policy initiatives.

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Senator Joseph I. Lieberman
Chairman, Subcommittee on Clean Air and Nuclear Regulation
Committee on Environment and Public Works
United States Senate
Washington DC 20510-6175

14 June 1994

Dear Senator Lieberman,

Thank you for your letter of May 23, where you included questions from yourself and Senators Faircloth and Lautenberg, as follow-up to my testimony on May 11 before your Subcommittee.

Attached to this letter are my answers to those questions.

Please do not hesitate to contact me if you or your colleagues have further questions.

Yours faithfully,

CRE Coggins

C.R.E. Coggins, Ph.D.
Principal Scientist

"We work for smokers."

RESPONSES BY DR. CHRIS COGGINS TO ADDITIONAL QUESTIONS

ADDITIONAL QUESTIONS BY SENATOR LIEBERMAN

Question. In your written testimony, you conclude that, "The EPA's approach, much less its conclusions, would not withstand real scientific peer review." The Science Advisory Board, an independent panel of 18 scientists, reviewed the EPA report and unanimously concluded that EPA was justified in categorizing ETS as a human lung carcinogen. The SAB also concurred with EPA's conclusion that ETS causes noncancer respiratory effects in adults and children. Why do you believe that the Science Advisory Board review was not a "real scientific peer review?"

Answer. I serve as a peer-reviewer for numerous scientific journals, *e.g.*, *Fundamental and Applied Toxicology.* I also am on the Editorial Board of the journal *Inhalation Toxicology.* Based on my experience and practice, scientific peer review should be a critical review of methods and data reported to determine if conclusions are valid. Here, the SAB reviewed the report, responded to specific questions raised by the EPA, and made recommendations on how to strengthen the report. The author(s) of the report—EPA—made the ultimate decisions regarding publication.

In my opinion as a peer reviewer, numerous flaws in the EPA report would prevent it from being published without significant modifications in a peer-review journal. Examples include EPA's questionable statistical techniques, the agency's failure to follow its own published guidelines for risk assessment, and the dredging of the data to achieve an apparently predetermined conclusion. The significant point here is that were EPA to modify the report to address these (as well as other) peer-review issues, in my opinion, a different conclusion should be reached.

The "unanimity" of opinion expressed by the SAB surprised me somewhat, especially considering comments raised during the SAB's public hearing in December 1990. For example, Dr. Kabat stated that "classifying ETS as a Class A carcinogen is maybe a little rash." I suspect that the SAB's unanimous endorsement of EPA's decision to classify ETS as a Class A carcinogen may be attributed somewhat to the "consensus syndrome" (which I discuss below).

One other point should be brought to the Subcommittee's attention. In 1993, at the Toxicology Forum's Annual Summer Meeting which I attended, Dr. Jan Stolwijk, the Vice Chair of the SAB, disclosed that the SAB tried to discourage EPA from publishing its quantitative risk assessment estimate that ETS accounts for 3,000 lung cancer deaths per year—principally because the estimate "has not a very firm basis". As Dr. Stolwijk pointed out, EPA's decision to publish the number in spite of the SAB's misgivings was a policy choice. That is a clear example of why the SAB process is not real scientific peer review.

Question 2. The National Academy of Sciences, U.S. Surgeons General, the Working Group on Passive Smoking—an independent international panel of scientists supported in part by RJR Reynolds Nabisco, and the National Institute for Occupational Safety and Health have all published studies that have concluded that ETS is associated with an increased risk of lung cancer and severe respiratory illnesses. Do you believe that the evidence on ETS and lung cancer contained in all of these studies does not support the conclusion that ETS is a human lung carcinogen or that ETS has serious respiratory effects? If so, why?

Answer. The groups mentioned did not publish studies, they issued reviews of the available data. They reviewed the same basic set of data, effectively subsets of the data contained in the EPA report.

My analysis of those data, as well as the analysis recently performed by the United States Library of Congress, Congressional Research Service, "Cigarette Taxes to Fund Health Care Reform: An Economic Analysis," Report 94–214E by Jane O. Gravelle and Dennis Zimmerman, March 8, 1994 (CRS), concludes that the data do not justify the conclusions made by the organizations referenced. The written statement that I submitted on behalf of The Tobacco Institute sets forth a detailed summary of the basis for my opinion that the available data do not show that ETS "is a proven lung carcinogen or that ETS has serious respiratory effects." In addition, the CRS concludes:

- "Our evaluation was that the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking."
- "The epidemiological evidence for passive-smoking-related disease is weak"
- "The combination of the greater statistical uncertainty of pasve-smoking epidemiology studies and the potential inconsistency of those results with physical exposure models is responsible for our conclusion that the finding of increased risk from passive smoking is uncertain"

- "The EPA study analyzed and summarized 30 studies of passive smoking lung cancer effects. Critics have questioned how a passive-smoking effect can be discerned from a group of 30 studies of which 6 found a statistically significant (but small) effect, 24 found no statistically significant effect, and 6 of the 24 found a passive smoking effect opposite to the expected relationship."
- "EPA attempted to standardize this diverse group of studies to account for statistically important differences in their methodologies. In this process, EPA reduced the standard for statistical significance from the usual standard, and the one generally used in the original studies. It is unusual to return to a study after the fact, lower the required significance level, and declare its results to be supportive rather than unsupported of the effect one's theory suggests should be present, but our conclusion about the uncertainty of the EPA results is not dependent upon this change in significance levels. However, the issue raised by the change in the statistical significance standard should not be ignored."
- "Two epidemiology studies that each covered a large number of observations were published in 1992 after the cutoff date for inclusion in the EPA report. The one with the largest number of observations found no overall increased risk of lung cancer among nonsmoking spouses of smokers, The other found an increased, but statistically not significant, lung cancer risk.
- "The existence of an exposure threshold for disease onset below which many passive smokers fall is not implausible. Most organisms have the capacity to cleanse themselves of some level of contaminants. It is for this reason that public policy usually does not insist that every unit of air or water pollution be removed from the environment; the damage of low levels of pollutants is sufficiently small (through the self-cleansing process) that removal is not cost effective."
- "These studies do not have (and indeed cannot have) very precise estimates of exposure from environmental tobacco smoke. The data are based on interviews of the subjects of their relatives. If errors in measurement occur in a systematic way that is correlated with development of the disease, the effect would be to bias the results. An example would be if those individuals who developed lung cancer (or relatives of those individuals) remembered or perceived their exposure differently from those who did not develop the disease."
- "In sum, this analysis suggests. . . . that the absence of controls or the inability to control for other factors may be a major problem in relying on epidemiological estimates of the health effects of passive smoking. To restate the criticism, if wives or children of smokers share in poor health habits or other factors that could contribute to illness, statistical associations found between disease and passive smoking could be incidental or misleading."

These criticisms are shared by other scientists and academics. For example, a recent article (Wall Street Journal, 6/3/94) by a Harvard professor of economics states "the statistical evidence for health risks from second-hand smoke is extremely weak, even by the standards of an empirical economist."

One other point should be emphasized. The fact that various organizations reach a similar conclusion does not by itself make the conclusion correct. The legitimacy of the "consensus syndrome" that permeates modern science is subject to serious questions. "Just as good government is based on formal law rather than individual opinions, good science depends on suitable methods and evidence, not on a consensus of authorities." (Feinstein, A., "Fraud Distortion, Delusion, and Consensus: The Problems of Human and Natural Deception in Epidemiologic Science," Am. J. Med. 84:475–478, 477 (1988).

Question 3. You have testified that the maximum amount of ETS to which a nonsmoker is exposed is equivalent to approximately 1–5 cigarettes per year. Did you determine this "cigarette equivalent" estimate using a physical extrapolation method that used cotinine as a biomarker to measure ETS exposure in nonsmokers? If so, are you aware of criticisms of this method, including those raised by the Surgeon General, which claim that it is flawed because nicotine is removed by the atmosphere very quickly and also because it does not measure the biological absorption of ETS constituents other than the biomarker? Are you aware of a 1986 Surgeon General report that concluded that this method is a "complex and potentially meaningless process." Isn't it possible for this approach to result in a higher "cigarette equivalent" estimate if different biomarkers for ETS exposure are used?

Answer. In my testimony, I quoted from an article published in 1993 by Dr. Larry C. Holcomb in Environment International ("Indoor Air Quality and Environmental Tobacco Smoke: Concentration and Exposure," vol. 19, pp 9–40). In that article, Dr. Holcomb reviewed published measurements of several ETS constituents made in hundreds of indoor environments. He calculated cigarette equivalents based on mean differences of respirable suspended particles (RSPs) between smoking and nonsmoking conditions. Dr. Holcomb noted: "The particle fraction of ETS is the portion on which the majority of the health claims concentrate. An estimate of the dose of ETS particles that persons receive would provide an independent assessment as to whether these health claims are realistic." He provided cigarette equivalent estimates for four scenarios, including maximal exposure. The ranges were from less than one to less than four cigarettes per year.

Dr. Holcomb further noted that the calculations have "little or no relevance to any assessment of the potential risk from exposure to ETS", but added that the calculations do "at least allow a subjective impression of the relative doses involved in active smoking compared to everyday exposure to ETS".

I agree that the concept of cigarette equivalents has limitations for assessment of the potential risk from ETS. In a recent public message published by R. J. Reynolds Tobacco Company, this limitation was noted. That message also pointed out that Reynolds does not believe that ETS is the same as the smoke a smoker inhales. (answer to question 13 submitted by Senator Faircloth.) In addition, the message noted that there are many ways to calculate cigarette equivalents. In order to gain a perspective on ETS exposure, the message presented cigarette equivalents based upon Dr. Holcomb's published average smoking area measurements of nicotine. Those calculations produce values which are higher than those based upon RSPs. They are:

> 1. In a month, a non-smoker living with a smoker would, on average be exposed to secondhand smoke equivalent to smoking approximately one and a half cigarettes.
>
> 2. In a month, a non-smoking waiter who works eight hours a day, 5 days a week in a restaurant would, on the average, be exposed to secondhand smoke equivalent to smoking about two cigarettes.
>
> 3.
>
> In a month in a modern office where smoking was permitted, a non-smoker sharing an office with a smoker would, on average, be exposed to the equivalent of smoking about one and a quarter cigarettes.

Neither the calculations I referred to in my testimony nor the calculations presented in Reynolds' public message were based upon cotinine. The question correctly notes that cotinine is a biomarker—that is, a metabolic product of nicotine. Cotinine measurements in body fluids, however, cannot in my opinion be used quantitatively to derive cigarette equivalents or to quantify precisely anyone's exposure to ETS. Cotinine is, at best, a qualitative marker of ETS exposure. Limitations arising from measurement techniques for cotinine, inter-individual metabolic differences, and the effects of dietary nicotine all make quantitative use of cotinine measurements unsuitable. Those particular limitations are not present when using area measurements of nicotine.

Although nicotine can be rapidly depleted from the air immediately following smoking, overall it tends to linger in an environment long after other ETS constituents have dissipated. Nelson, P.R., *et al.*, "Effect of Ventilation and Sampling Time on Environmental Tobacco Smoke Component Ratios", 26 Environmental Science & Technology 1909–1915 (1992).

The EPA has stated nicotine, though not ideal, is a "good" and "attractive" marker for estimating the contribution of ETS to indoor air for a variety of reasons. Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders, Dec. 1992, EPA/600/6–90/06F at page 3–20.

In its recent Notice of Proposed Rulemaking on indoor air quality, OSHA noted that "[f]ield studies have also shown that vapor phase nicotine concentrations are correlated with the number of cigarettes smoked. . . .," 59 Federal Register 15990.

In responding to the question put to me at the May 11 hearing, I attempted to note the difficulties of making a direct extrapolation from ETS to cigarette equivalents. As our company noted in its public message, use of other compounds may give different results, as the comparison between Dr. Holcomb's calculations and the calculations in that message demonstrate. Recently, some have put forward estimates of cigarette equivalents based on other markers ranging from 40 cigarettes a day to 10 cigarettes per hour. It defies common sense to imagine that nonsmokers could be inhaling over twice the amount that smokers inhale when ETS is hundreds to thousands of times more dilute than is mainstream smoke.

Question 4. In your written testimony, you write: "at least a 95 percent confidence level is required in epidemiologic studies to conclude that an association is statisically significant. Does a two-tailed statistical test that has a 95 percent confidence interval achieve the same level of statistical significance as a one-tailed statistical test that has a 90 percent confidence interval? If so, why do you testify that a 90 percent confidence level is unorthodox if it achieves the same level of statistical significance as a two-tailed test? Are you aware of the circumstances when a one-tailed statistical test is used instead of a two-tailed test? If so, please explain those circumstances. Wasn't EPA's use of a one-tailed test warranted given the prior evidence that suggests that tobacco smoke causes lung cancer?

Answer. This issue has been a point of confusion for some time, and I believe that the first question as posed is in fact incorrect. I think the question should be "does a two-tailed statistical test that has a 90 percent confidence level achieve the same level of statistical significance as a one-tailed test that has a 95 percent confidence level? ". While the answer to this question is "yes" in a very technical statistical sense, the revealing point is that EPA changed statistical procedures midstream. Scientifically, this approach is inappropriate for the reasons provided below. More significant, in a highly unusual gambit the EPA changed the limits for confidence intervals from 95 percent in their earlier drafts to 90 percent in their final report. Such a procedure amounts to simply "moving the goalposts closer". Scientifically, it is totally inappropriate to change the limits after realizing that the intended results would not be significant with conventional limits. The CRS also criticizes this maneuvering by EPA:

> EPA attempted to standardize this diverse group of studies to account for statistically important differences in their methodologies. In this process, EPA reduced the standard for statistical significance from the usual standard, and the one generally used in the original studies. It is unusual to return to a study after the fact, lower the required significance level, and declare its results to be supportive rather than unsupported of the effect one's theory suggests should be present, but our conclusion about the "uncertainty" of the EPA results is not dependent upon this change in significance levels. However, the issue raised by the change in the statistical significance standard should not be ignored.

To address this issue adequately, two intermingled issues must be explained: confidence limits (related to confidence intervals) and number of tails (related to tests of significance).

- An odds ratio or relative risk should always be quoted with "confidence limits" around it to give a "band" in which we are reasonably confident the relative risk point estimate lies. The standard level for a confidence limit is 95 percent; we accept a possibility of 1 in 20 that our estimate of the odds ratio being within the fixed confidence limits could be wrong. The use of a 90 percent confidence limit doubles that accepted error: here we accept a possibility of 1 in 10 that our estimate of the odds ratio being within the fixed confidence limits is wrong. 95 percent confidence limits were employed in 27 of the 30 studies and in 10 of the 11 American studies reviewed by the EPA. In altering the original analyses, the EPA doubled the possibility that any statistically significant association is simply a random and meaningless event.
- Significance tests are performed to see if the odds ratio obtained, along with the variability in the data, is significantly different from unity (or 1.0). The standard method for performing this comparison is to use what is called a two-tailed test: we examine whether the odds ratio obtained is higher or lower than unity. The use of a one-tailed test simply tests whether the odds ratio is higher than unity, or lower than unity, but not both. The use of the one-tailed test assumes that any change will be in one direction only.
- One-tailed tests are acceptable under certain circumstances, but *never* after one has examined the data and determined the direction of the change. The EPA's justification for the retrospective use of a one-tailed test is inadequate: the agency claims that any "beneficial" or protective effect of exposure to ETS on lung cancer is unrealistic. This claim, or assumption, is not valid in light of published epidemiologic data. One of the 30 worldwide studies, the study performed by Wu-Williams, did indeed show an apparent protective effect (the point estimate for the odds ratio was significantly less than 1.0). Five other studies also had odds ratios that were less than 1.0, but these values did not reach statistical significance. In other words, the EPA reviewed studies that reported results going in both directions. The agency's "decision" to assume that the odds ratio could go in only one direction is scientifically improper.
- EPA further rationalizes the use of the one-tailed test because of the relationship between active cigarette smoking and lung cancer. The strained logic here assumes (a) that mainstream smoke and ETS are the same, and (b) that there is a linear extrapolation between the amounts of this similar material from mainstream to ETS. These assumptions are not valid, and many of the groups referenced in question 1 above recognize this fact. For example, the Na-

tional Academy of Sciences wrote in its 1986 review of ETS: "[b]ecause the physicochemical nature of ETS, MS and SS differ, the extrapolation of health effects from studies of MS or of active smokers to nonsmokers exposed to ETS may not be appropriate."

- In these circumstances, it is my opinion that EPA's convenient use of 90 percent, one-tailed statistical tests is improper.

Question 5. Do you believe that EPA's conclusions regarding the noncancer respiratory health effects of ETS on adults and children are consistent with the weight of the evidence? If no, what are your specific objections to these EPA conclusions and the analyses on which they are based? Do you believe that there are any noncancer respiratory health effects of ETS? If so, please state those effects and the magnitude of any non-cancer health effects that you believe exist.

Answer. The EPA's conclusions regarding the noncancer respiratory health effects of ETS are not appropriate. In a review article published earlier this year, Tredaniel Cal. explained that "No definite conclusion can be drawn from the studies that have investigated chronic respiratory symptoms in relation to ETS exposure. It remains controversial whether acute passive smoking is associated with important pulmonary physiological hazards." Tredaniel, *et al.*, "'Exposure to Environmental Tobacco Smoke and Adult Non-neoplastic Respiratory Disease," *Eur. Respir. J.* 7:173–185 (1994). These scientists pointed out a number of possible sources of bias and confounders that need to be examined in these types of studies.

The EPA reached only tentative conclusions regarding the noncancer respiratory health effects of ETS on children. The EPA said: "There is *some* evidence that the incidence of acute upper respiratory tract illnesses and acute middle ear infections *may* be more common in children exposed to ETS. However, several studies have failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism *preclude more definitive conclusions"* (emphasis added).

The range of respiratory problems for children are extremely multifactorial in nature. Published risk factors include: socioeconomic status, gas stove usage, family health history, family size, gender, age, indoor pollution, day bare use, animal exposures, stress, dampness/cold, winter season, occupational exposures, nutritional status and maternal smoking during pregnancy (preschool only for the latter). Few of the papers on ETS exposures in children control for more than a few of these factors, which means that the results obtained could easily be the result of factors other than ETS.

A recent review (Gross, 1993) concluded: "Several studies have suggested that a multiplicity of variables, acting together or acting simultaneously, could influence the outcome of epidemiologic studies and the respiratory health of children". The review goes on: "The possibility of interactions of confounding variables where the outcome could be of greater magnitude than that predicted on the basis of individual effects, and thus could influence associations attributed to ETS, has received little attention to date".

Concerning asthma, the EPA stated that "the evidence is suggestive, but not conclusive, of a causal association". Some studies have shown a statistically significant relation between passive smoking and childhood asthma, but more have not. Very recent work from the University of Virginia at Charlottesville found "no correlation between active or passive smoking and acute asthma". Those investigated stated that they were not convinced that ETS is "an important risk factor for the development of asthma".

Regarding sudden infant death syndrome (SIDS), the EPA has the following to say: "The view of the fact that the cause of SIDS is still unknown, it is not possible to assess the biological plausibility of the increased incidence of SIDS related to ETS exposure. Consequently, at this time this report is unable to assert whether or not passive smoking is a risk factor for SIDS".

The health problem that is currently the subject of many statements from the antismoking industry is a link between ETS exposure and cardiovascular disease. There are relatively few epidemiology studies on this purported link, and those that do exist do not control adequately for confounding factors. The overall odds ratio (from a questionable meta-analysis) of 1.3 is very similar to that for mainstream smoke at 1.7, which is scientifically implausible given that ETS is hundreds to thousands of times more diluted than is mainstream smoke. Researchers in California (Glantz and Parmley) attribute 37,000 cardiovascular disease deaths to second-hand smoke, but even the EPA questions the heart disease claims. Robert Axelrad, head of EPA's Indoor Air Division, has said that: ". . . the estimated association between second-hand smoke and coronary heart disease may be a figment of Stan Glantz's imagination and William Parmley's imagination . . ." Dr. Brockie of the University of Texas said the pooled relative risk reported by Glantz and Parmley "was in fact very weak, at 1.3. At this level of risk there are at least 300 or more reported risk factors for cardiovascular disease."

Question 6. You have testified that EPA did not rule out confounding factors, such as diet, when analyzing the epidemiologic data on which EPA's conclusion that ETS is a human lung carcinogen is based. As a result, you state that confounding cannot be ruled out as an explanation for the reported association between spousal smoking and lung cancer risk. If your contention is true, wouldn't the studies' results differ depending upon the country in which they were conducted and the confounding factors associated with that country? For example, you testified that a high-fat diet is associated with a high risk of lung cancer, yet the studies showed a consistent increase in lung cancer was associated with ETS exposure both in countries where the people eat a low-fat diet as well as countries where the people eat a high-fat diet. If your contention is true, how do you explain that analyses of the 30 studies produced consistent dose-response relationships between ETS exposure and lung cancer although they were conducted in countries where confounding factors vary?

Answer. The studies did not produce consistent dose-response relationships between ETS exposure and lung cancer. Several studies show a reverse dose-response trend, i.e., higher reported levels of spousal smoking are associated with an apparent decreased risk of lung cancer. One of these studies reported a reverse dose response that was statistically significant.

Contrary to the assertions by EPA and others, the epidemiologic studies of ETS and spousal smoking are quite *inconsistent*. The results vary widely by geographic area and the magnitudes of the reported associations vary by almost 300 percent. Without considering the requirement of statistical significance, six studies report point estimates of the odds ratio above 2.0 while six studies report point estimates of the odds ratio below 1.0.

A comparison of results between countries/regions also shows these inconsistencies. A meta-analysis of the risk reported for the Chinese studies is statistically different from that reported for the European studies. This difference is highly statistically significant—indicating that the difference cannot be ascribed to chance. The inconsistency in the country specific summary relative risks weighs against the causal interpretation of the reported associations. Interestingly, Chinese studies report the *lowest* summary risk for any country group.

Generally, the higher reported odds ratios come from early studies, studies that were performed without attempts to gather information about confounders. Very few of the studies (especially the earlier ones) were actually designed to study ETS. The more modern studies correct for more confounders and in general they show no increase in risk as a result of exposure to ETS.

Diet is, of course, only one of many known confounding factors for lung cancer (other risk factors include mainstream smoke, age, radon, familial factors, industrial exposures to materials such as chloromethyl ethers, previous lung disease, air pollution, asbestos, heavy metals such as arsenic and nickel, and diesel exhaust), and its importance has been recently confirmed. I am referring to the work by Brownson *et al.*, using 432 nonsmoking women, married to smokers, in Missouri. We do not know whether factors such as genetic makeup, other dietary factors, local customs, etc. could interact with the varying fat content in the diets in the non-US studies.

7. Do statistical measures, such as consistency, dose response, and specificity, suggest that a causal relationship exists in epidemiologic data? If so, using these measures, do the results of the 30 epidemiologic studies suggest that a causal relationship exists between ETS and lung cancer?

In my opinion, statistical associations do not prove causation. And the epidemiologic data relating to ETS and lung cancer certainly do not justify a causal inference. Any association between ETS and lung cancer is certainly weak at best. The 30 ETS studies reviewed by EPA produced odds ratios that were maximally around 2½ with an arithmetic mean that is around 1½. Odds ratios less than about 3 are considered to be very weak, and are highly susceptible to bias and confounding.

The results of the epidemiologic studies are plainly inconsistent. According to the CRS, "The EPA study analyzed and summarized 30 studies of passive smoking lung cancer effects. Critics have questioned how a passive-smoking effect can be discerned from a group of 30 studies of which 6 found a statistically significant (but small) effect, 24 found no statistically significant effect, and 6 of the 24 found a passive smoking effect opposite to the expected relationship."

No positive dose-response relationship has been reported. As noted in my response to question 6, the studies did not produce consistent dose-response relationships between ETS exposure and lung cancer. In fact, *none* of the 30 studies shows a statistically significant monotonic dose-response relationship. Several studies show a reverse dose-response, *i.e.*, higher reported levels of spousal smoking are associated with an apparent decreased risk of lung cancer. One of these studies reported a reverse dose response that was statistically significant.

Many of the studies that showed a dose-relationship had responses that were "nonmonotonic". In other words, the response did not always increase with increasing dose. This is contrary to what one would expect if a dose-response relationship truly exists. Other studies showed lower risks for consumption of "more than a pack a day" than for "less than a pack per day".

One of the most striking aspects of EPA's dose-response analysis is that no measurements of ETS were made in any of the studies, and about half of the people that say that they were married to smokers were not in fact ever exposed. We do not know whether the so-called high-dose groups were exposed or not to high doses.

ADDITIONAL QUESTIONS BY SENATOR LAUTENBERG

At the end of your written statement, you say the following "viewed objectively, the EPA's conclusions about ETS are based on weak and contradictory evidence and selective arguments." You go on to say, "The EPA report simply does not provide a sound basis for public policy initiative."

Question 1. Why should anyone believe that your views on the dangers of ETS are objective?

Answer. I am a scientist. Science is based on methods and data, not perceptions, bias, ad hominem judgments and not consensus. The data relating to ETS speak for themselves. As noted earlier, I serve as a peer-reviewer for a number of scientific journals, and I serve on the Editorial Board of one journal. I also am a board certified toxicologist who has published numerous articles on tobacco and tobacco smoke in the peer review literature. Certainly the CRS cannot be accused of bias in favor of the tobacco industry. The CRS reached conclusions similar to mine.

Question 2. Are you not employed by R.J. Reynolds? Don't they pay your salary?

Answer. Yes.

Question 3. If fewer and fewer teenagers began to smoke each year and millions quit smoking, wouldn't R-J. Reynolds' revenues and profits go down? Then you have a financial interest in making sure that people continue to smoke?

Answer. I am not involved in the marketing area, but I know that our company supports the laws in every state that prohibit kids under 18 from buying cigarettes. We do not want kids to smoke. We are always blamed if they do, and that can lead to restrictions on our ability to communicate with adults who choose to smoke. I also think that the question, as stated, includes questionable premises and oversimplifies the sales and marketing issues. I do know that revenue and profits depend on a variety of factors, including price and costs, so the formula this question presents simply is not correct.

Question 4. Has the R.J. Reynolds company ever conducted research on the health effects of tobacco products on animals?

Answer. Since I joined the company in 1985, we have performed inhalation studies on rats and mice to evaluate the biological activity of our products.

Question 5. Has RJ. Reynolds company sharėd all of this information, including non-published data, with the Federal government?

Answer. Since I joined the company in 1985, we have made available to the public the results of studies that do not relate to proprietary product development research or patentable ideas, and that otherwise contribute to the scientific literature and are of publishable quality. In fact, in addition to making a number of publications of our rodent inhalation research, we have donated actual tissues to the United States Armed Forces Institute of Pathology so that other researchers can independently evaluate our conclusions.

Question 6. Has the RJ. Reynolds company ever conducted any type of smoking inhalation study on animals, either direct smoking or indirect smoking?

Answer. As noted above, since I joined the company in 1985, we have performed inhalation studies using rats and mice. These studies have related both to active smoking and to environmental tobacco smoke.

Question 7. Has the R.J. Reynolds company ever contracted out research on the effects of tobacco products on animals?

Answer. Since I joined the company in 1985, I am aware that the company has contracted out research on the biological activity of tobacco products on rodents.

Question 8. Has the RJ. Reynolds company ever conducted research on the effects of tobacco on humans?

Answer. Since I joined the company in 1985, I am aware that the Company has performed research on human responses to exposure to tobacco smoke, *e.g.*, certain sensory responses.

Question 9. Has the RJ. Reynolds company conducted research on environmental tobacco smoke?

Answer. Yes.

Question 10. Would you share all of the non-published animal data on the health effects of smoking with this Committee?

Answer. I do not have the authority to speak for the Company on issues such as this one. However, I believe that R. J. Reynolds would cooperate in an appropriate fashion with this Subcommittee, subject to adequate protection for competitively sensitive information.

Question 11. If not, would you provide it to this Committee if it was subpoenaed?

Answer. See answer to question 10 above.

Question 12. Does R.J. Reynolds contract out research on the health effects of smoking? If so, why? Is it to shield this information from U.S. courts and the Congress?

Answer. As noted above, the research and development department at R.J. Reynolds Tobacco Company contracts research to outside entities for a number of reasons. Some contract research might relate to areas that are relevant to the smoking and health question. In my experience, the Company has not contracted out research to shield it from the United States courts or the Congress.

Question 13. Do you have paper shredders in the research buildings at R.J. Reynolds? If so, why?

Answer. We maintain paper shredders at the research department to shred unnecessary paper. Every research institution I have ever visited (whether industry or academic) maintains paper shredders. Most of the shredded paper (e.g., all non-colored paper) is sent to a contract recycling facility.

ADDITIONAL QUESTIONS BY SENATOR FAIRCLOTH

Brownson Study

Question 1. What section of a scientific study presents actual data and the authors' analysis of the actual data?

Answer. It is normal for reports of scientific studies to be divided into the following sections: Introduction, Materials and Methods, Results, Discussion and References. Some journals also request an Abstract and sometimes a Conclusions section.

The Results section contains the actual data; the Discussion section contains the author's analysis of the data.

The Abstract is usually very limited in length: in the journal in which the Brownson study is published the American Journal of Public Health, the Abstract's length is limited to "780 words set out under four heads: Objectives (hypotheses, etc.), Methods (design, population, analysis), Results and Conclusions."

Question 2. Is there any portion of a study where the author is allowed to bring in any personal opinions or views beyond the scope of the data presented in the study?

Answer. It is usual for authors in their Discussion of the data they obtained to review the potential impact of their findings, and to compare their findings with other work that has been published.

Opinions or views that are clearly beyond the scope of the data presented in the study should be eliminated in the peer-review process (where the manuscript is reviewed by other scientists, who make recommendations on whether the paper is acceptable for publication). However, the peer-review process depends very much on the Editor and on the reviewers he selects. It is certainly possible for the peer-review process to be bypassed, particularly if the issue is contentious and if the results conform to a view held by the Editor.

Question 3. So, when Senator Lautenberg referred to the statement by Ross Brownson in his paper that advocates restrictions of smoking in public places, was that actual data or the author's personal opinion?

Answer. The Conclusions section of the Abstract of the Brownson paper reads: "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking. Comprehensive actions to limit smoking in public places and worksites are well advised."

The first sentence of this Abstract is not accurate, based on the data reported. Table 2 of the study reports 28 odds ratios for the relationship between passive smoke exposure during adulthood and lung cancer. None of the reported odds ratios reach statistical significance, the traditional procedure scientists use to determine if the results are truly meaningful.

The second sentence in the Abstract is clearly a policy statement. It is highly unusual for scientific papers to include such a statement, especially as the statement appeared in such a highly conspicuous position. More important, however, is the fact that the policy opinion is not justified by the data presented in the-paper.

Question 4. In your opinion, do the actual data presented by Brownson support proposed regulation of smoking in public places? why or why not?

Answer. The data presented in the Brownson paper do not support proposed regulation of smoking in public places.

EPA

Question 5. Did the EPA do any original research in support of its risk assessment?

Answer. The EPA did not do any original research in support of its risk assessment; instead, the agency performed statistical analyses on the results of published epidemiologic studies. Neither of the two EPA authors is an epidemiologist.

Specifically, the EPA examined 30 worldwide epidemiology studies (epidemiology being defined as the statistical examination of disease rates in human populations), and the agency examined in a meta-analysis a selected set of American studies.

The EPA also reviewed some published animal studies and examined published reports on the possible relationship between ETS exposure and diseases other than lung cancer.

Question 6. Did the EPA report conduct a meta-analysis on workplace data?

Answer. The EPA did not conduct a meta-analysis on workplace data. The EPA restricted its meta-analysis to published studies of women "married to or living with a smoker".

A recent publication does contain an analysis of workplace data. Lee (Chapter 2, Table 5 in "Environmental Tobacco Smoke", Springer-Verlag, New York, 1993) performed a meta-analysis of 14 published workplace studies, and using 4 different sets of assumptions, found an overall odds ratio that was at most 1.08. None of the meta-analysis odds ratios calculated by Lee for workplace exposure were statistically significant.

Question 7. Could you explain the misclassification issue? Is it possible that errors in EPA's handling of misclassification could nullity EPA's conclusions regarding ETS?

Answer. In studies of ETS and lung cancer, comparisons are usually made of never smokers married to smokers, with never smokers married to nonsmokers. Misclassification refers to that proportion of stated "never smokers", who are in fact smokers. Stated differently, misclassification bias refers to the tendency of smokers to misrepresent themselves as nonsmokers. In 1986, Stellman, a scientist with the American Cancer Society, recognized the importance of misclassification bias: "Some of the passive smoking studies which have been published might have a great deal of misclassification bias, in exposure and in results."

The EPA accepted that misclassification does occur, and used a figure of 1.09 percent. This figure was curious, because it was apparently based on an unpublished model that contains mathematical and conceptual inconsistencies. It also is clearly too low. Other published work has shown that for the United States population the actual figure is closer to 6 percent. EPA was aware of these differences, but selected the lower figure.

As the misclassification rate increases, the odds ratio decreases. In the EPA's meta-analysis of the 11 U.S. studies, a misclassification rate of 3.05 percent is sufficient to render the overall odds ratio not statistically significant—even at the EPA's 90 percent confidence level.

Regarding misclassification, the CRS states ". . . .it remains possible that a relationship observed might reflect the effects of active rather than passive smoking."

Question 8. If the EPA had consistently utilized a 95 percent confidence interval and if the EPA had included the data from the then available Brownson and Stockwell studies, what impact would these measures have had on EPA's meta-analysis and its conclusions?

Answer If EPA had consistently utilized the standard 95 percent confidence level, and if EPA had included in the meta-analysis of US studies the data from the then available Brownson and Stockwell studies, then the resulting overall odds ratios would not be statistically significant.

Question 9. From a scientific standpoint, is there any justification for the EPA excluding the data from the Brownson and Stockwell studies?

Answer. There is no scientific justification for excluding the data from the Brownson and Stockwell studies. The justification offered by the EPA for exclusion is that the studies were published after the EPA's cut-off date. That is a logistics decision, not a scientific justification. It also should be pointed out that EPA was aware of both studies well before publication of the final report.

There is scientific justification for the inclusion of the data from the Brownson and Stockwell studies into the meta-analysis. Adding these two large studies from the National Cancer Institute almost doubles the overall number of lung cancer cases in the meta-analysis. Seven of the 11 studies used in the EPA's meta-analysis had less than 50 cases.

Regarding the Brownson and Stockwell studies, the CRS report states: "Two epidemiology studies that each covered a large number of observations were published in 1992 after the cutoff date for inclusion in the EPA report. The one with the largest number of observations found no overall increased risk of lung cancer among nonsmoking spouses of smokers, the other found an increased but statistically not significant, lung cancer risk"

Question 10. Was the Fontham study a final study? Are there problems with including an incomplete, ongoing study?

Answer. The initial study by Fontham, published in November 1991 and included in the EPA's meta-analysis, was incomplete. The authors state "this preliminary report includes cases diagnosed through the first 3 years of a 5-year study."Inclusion of this study by EPA and the study itself were criticized.

It would seem to me that if EPA were willing to include an interim report in its meta-analysis, the agency also should be willing to include the two final reports by Brownson and Stockwell. As discussed below, had EPA done this, the summary relative risk would have gone down and would not have been significant.

Since I received these questions, the final report of the Fontham study was released. This report was hailed by some as something "new" and significant. When the study is examined, however, a very different picture emerges. Let me state just a few examples.

The Fontham study is not new. It is merely an update of the interim Fontham study which at the time was one of the 11 published studies of nonsmoking U.S. women that attempted to estimate the potential risk of lung cancer that might be attributed to ETS exposure. None of these 11 studies measured actual ETS exposure. The Fontham study remains unique in being the *only* study ever to find a statistically significant overall elevation in risk attributed to ETS exposure in either the home or the workplace for U.S. women. That was true when the EPA included the interim study in its meta-analysis. It is true today.

Fontham's 1994 findings do not differ significantly from the 1991 results. The relative risk (RR) attributed to household ETS exposure rose marginally from 1.21 to 1.23, and remains nonsignificant; the RR attributed to occupational ETS exposure rose from 1.34 to 1.39 and remains significant; the RR attributed to social ETS exposure fell from 1.58 to 1.50 and remains significant; and the RR attributed to spousal ETS exposure rose from 1.21 to 1.29 and became significant. Serious questions about the study continue to exist, e.g., the selection of subjects and the role of confounders.

Substitution of Fontham's 1994 results (for her 1991 interim results) in EPA's analysis (without correction of any of the errors by EPA that inflated its estimate) increases the meta-analytic RR slightly—from 1.19 to 1.20. But, if the Brownson, A. 1992 and Stockwell, A. 1992 results (that were published prior to publication of EPA's analysis) are also added, the meta-analytic RR decreases to 1.11, a nonsignificant value. EPA would not have obtained a "significant' risk estimate in 1992 without Fontham's interim results. *Now*, even with Fontham's final results, and with the inclusion of the Brownson and Stockwell studies, the risk estimate becomes nonsignificant.

Fontham should be compared to the NCI's 1992 Brownson, A. study. That study examined 432 never-smoker and 186 former-smoker Missouri women with lung cancer (a total of 618 cases). Brownson found no increase in risk of lung cancer due to ETS exposure in either the home or the workplace, no increase in risk attributed to exposure to ETS in childhood, nor any evidence of an interaction between childhood and adulthood ETS exposures. Fontham's results are almost totally inconsistent with Brownson's and with the body of evidence from other U.S. spousal studies.

Question 11. Does the EPA, or even OSHA for that matter, operate on a no-exposure, no safe threshold basis for alleged carcinogens? Is such an approach scientifically justifiable?

Answer. I believe the no-threshold basis for alleged carcinogens ignores the wealth of data accumulated over the years and is not scientifically justified. Although EPA's Risk Assessment Guidelines assume that any level of exposure to alleged carcinogens carries a potential risk of cancer, neither EPA nor OSHA operates on the basis of totally eliminating all exposure to substances regulated by those agencies. As noted in a textbook entitled *Minimis Risk*:

> The Supreme Court and some other federal courts have recently exhorted agencies to consider the significance of risk findings in cases involving OSHA, EPA, and FDA. EPA has sought to establish trigger levels for regulatory action in areas such as hazardous waste cleanup or control of carcinogens, and has frequently,, designated specific risk levels as being "below regulatory concern."

Fiksel, J., "De Minimis Risk: From Concept to Practice" in *De Minimis Risk*, Plenum Press, 1987 (C. Whipple ed.), at 3–4. Indeed, as I explained in my oral testimony, EPA permits some level of arsenic—a Class A carcinogen—in drinking water.

As I understand the process, when EPA and OSHA regulate, each agency typically establishes permissible exposure limits (PELs). Thus, for example OSHA has established an exposure limit of 1 ppm (part per million) as a time-weighted average occupational exposure for formaldehyde (designated as a carcinogen by OSHA), with a short term exposure level of 2 ppm.

In my opinion, the establishment of exposure limits is scientifically justifiable on several counts. Although the agencies generally make the default assumption of no threshold limits for carcinogens, that view is the subject of current and continuing debate in the scientific community. Moreover, even if the default assumption is accepted, it has been noted that "carcinogenic potencies. . . . are known to vary on a weight basis, by a range of 1 billionfold." Flamm, W.G. *etal.*, "Carcinogenic Potencies and Establishment of a Threshold of Regulation for Food Contact Substances, " in *De Minimis Risk*, at 88.

Question 12. Could you detail and summarize your scientific views on why this legislation should or should not be enacted?

Answer. The legislation before the Subcommittee is apparently premised on the belief that nonsmokers must be shielded from exposure to any amount of ETS in order to protect them from adverse health effects. My scientific views on why the legislation is unnecessary are set forth in my written statement to the Subcommittee, in my oral testimony, and in my answers to many of the questions submitted to me by members of the Subcommittee. There are obvious disagreements about the strength (and weakness) of the scientific evidence. But even if one were to accept the notion that ETS exposure carries a risk of adverse health effects, I believe the comments made in a recent article in EPA Journal should be of interest to the Subcommittee[1]:

> The irony in the current debate over indoor air pollution is that indoor air fits the classic case where economists argue government intervention is most unwelcome. By definition, indoor air is air within a building that someone owns. As long as someone owns the air, he or she obtains both the benefits and the costs from deciding how clean it should be.
>
> Individuals undoubtedly make mistakes, but the government must find some way of distinguishing whether people are underestimating the risks of their actions or are simply attaching different values to things than regulators do. . . . . Any honest appraisal would also have to admit that the government also makes its share of mistakes. As examples, consider the mandates for use of oxygenated auto fuels during the winter or for asbestos removal from buildings, or the Food and Drug Administration's restrictions on vitamins over the past 30 years.
>
> Government regulation of indoor air quality in office buildings and restaurants is similarly unwarranted, for there is still one person—the owner—who has clear incentives to do the best possible cost-benefit analysis. The question of allowing smoking in a restaurant is no different than the question

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[1] Hansen, R.G. and Lott, J.R., Jr. "Regulating IAQ: The Economist's View, "EPA Journal vol. 19, no. 4, pp. 30–31(1993)

> whether the restaurant provides music or other amenities. . . . . If restaurants do not provide the service wanted by the customers, they will go out of business.
>
> Similar considerations apply to employers and employees. For employees, there is a large economics literature identifying the higher wages firms must pay their workers in order for these workers to be willing to undertake riskier activities. Firms requiring that their workers inhabit so-called "sick buildings" not only face greater costs through higher absenteeism, but also higher wage costs as workers find those jobs less desirable places to be. Workers value their health, but they also value higher wages. It is not obvious who, other than the workers and owners, is in a better position to judge the trade-offs that workers are willing to make between these two values.
>
> The bottom line is that even the most efficiency-motivated government is unable to improve upon the cost-benefit calculus done by those affected by indoor air pollution In the real world the the choice is even clearer. Governments face many conflicting interests that have nothing to do with maximizing consumer or worker welfare. Government bureaucrats' preferences are not necessarily superior to those they are regulating. Who is to say that citizens are making mistakes whenever their decisions differ from what regulators desire?

Question 13. Could you explain in detail any quantitative or qualitative differences between mainstream smoke and ETS?

Answer. ETS is not the equivalent of mainstream smoke (MS), nor is it simply a quantitative variant of mainstream smoke. Claims that ETS is "more dangerous" than mainstream smoke because ETS is essentially the same as sidestream smoke (SS) are also incorrect. ETS differs significantly both from sidestream smoke alone and from a simple combination of sidestream smoke and exhaled mainstream smoke. ETS is "an aged, dilute mixture of sidestream and exhaled mainstream smoke from combustion of tobacco products such as cigarettes, cigars, etc." (Ogden, 1988, p. 77).

One scientist who has studied cigarette combustion processes and cigarette smoke generation for more than two decades, has stated, "Several scientists have incorrectly assumed that concentrated, fresh 55 is the same as ETS and have consequently made invalid conclusions concerning the properties of ETS" (Baker, 1989, p. 2). EPA scientists have themselves recognized that "ETS differs both chemically and physically from the precursor sidestream smoke, presumably due to chemical and physical transformations that occur as the mixture is diluted and aged" (Lofroth, 1989, p. 610).

ETS is a dynamic mixture of aged and diluted 55 and exhaled MS. "[O]nce the smoke has left the cigarette, cigar or pipe, its physical nature and relative chemical composition will change dramatically" (Proctor, 1988, p. 58). During aging, chemical reactions and physical processes change the chemical composition as well as the distribution of compounds between gaseous and particulate phases.

> A variety of studies have shown that nicotine in ETS is almost entirely in the vapor phase. This contrasts sharply to fresh mainstream smoke where nicotine is almost entirely in the particulate phase, and to exhaled mainstream smoke where there is actually little nicotine left. In fresh sidestream smoke, about 80 percent of the nicotine is in the vapor phase. Thus, as sidestream smoke is diluted and ages to form ETS, nicotine evaporates out of the particles. Other quite different studies have shown that matter evaporates from sidestream particles as they age to ET& Ingebrethsen has estimated that 20–30 percent of the original matter in sidestream smoke particulates is lost in this way. This is accompanied by a shrinkage of the particles.
>
> In addition to physical changes, chemical changes also occur as ETS ages. Thus, for example, nitric oxide slowly oxidizes over minutes and hours to nitrogen dioxide in ETS. However, these chemical changes, and indeed the particle size changes described above, will be far outweighed by the physical effects of air movement which occur in real indoor environments. (Baker, 1989, p.5.)

Some studies (Mahajan, 1990; Oldaker, 1989) indicate that ETS is diluted 100- to 1000-fold, compared to sidestream smoke. Actual ETS constituent concentrations often fall below detection limits of current scientific detection techniques (Carson, 1988; Crouse, 1989; Oldaker, 1990a; 1990b; Oldaker, 1986). Consequently, characterization of ETS by relying solely on sidestream smoke and mainstream smoke data is fallacious.

The following statement on "what is ETS?" was made by Huber (1992):

> Mainstream smoke is the tobacco smoke that is drawn through the butt end of the cigarette during active smoking; this is the tobacco smoke that the active smoker inhales into his or her lungs. Sidestream smoke is the tobacco smoke that the tobacco smoke that is released into the surrounding environment of the

> burning cigarette from is smoldering tip between active puffs. Many publications have treated sidestream smoke and ETS as if they were one and the same, but sidestream smoke and ETS are clearly not the same thing. Sidestream smoke and ETS have different physical properties and they have different chemical properties. Environmental tobacco smoke is usually defined as a combination of highly diluted sidestream smoke plus a smaller amount of that residual mainstream smoke that is exhaled and nor retained by the smoker.

Huber goes on: "In comparison to mainstream smoke and sidestream smoke, ETS is so highly diluted that it is not even appropriate to call it smoke, in the conventional sense. ETS . . . . consists of only a limited number of "remnants" or residual constituents present in highly dilute concentrations."

In short, there are fundamental physical and quantitative chemical differences among ETS and mainstream/sidestream smoke: the three are not equivalent, nor is ETS exposure a quantitative variant of cigarette smoking. The Surgeon General concluded in 1986 that "comparison of the relative concentrations of various components of sidestream smoke and mainstream smoke provides limited insights concerning the toxicologic potential of ETS in comparison with active smoking." The National Research Council of the National Academy of Sciences reached a similar conclusion: "[T]he smokes of MS, 55, and ETS differ, as the result of changes in the concentrations of individual constituents, the phase (particulate or vapor) in which the constituents are present, and various secondary reactions that chemically and physically alter ("age") the composition of the smoke. . . . . Because the physicochemical nature of ETS, MS, and 55 differ, the extrapolation of health effects from studies of MS or of active smokers to nonsmokers exposed to ETS may not be appropriate."

Any effort to extrapolate claimed health effects of mainstream smoke to ETS is demonstrably incorrect. The animal studies that I performed, and which I described in my May 11 testimony, used aged and diluted sidestream smoke as a surrogate for ETS. No meaningful changes were produced in these studies, even though massive concentrations were used for extended periods of time. The EPA refused to consider this series of work.

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STATEMENT OF DR. AUBREY E. TAYLOR, ON BEHALF OF THE COALITION ON SMOKING OR HEALTH

Mr. Chairman, and members of the subcommittee, I am Dr. Aubrey Taylor, chairman and Professor of physiology at the University of South Alabama College of Medicine in Mobile, Alabama. I am a specialist in the study of respiratory physiology. Day-to-day I study human respiratory processes and activities, particularly those related to lung and cardiovascular diseases, including heart attack and stroke. Today, I appear on behalf of the American Lung Association, the American Cancer Society and the American Heart Association, united as the Coalition on Smoking OR Health.

The Coalition on Smoking OR Health was formed in 1982. For the past 12 years, the Coalition has worked to educate public policy leaders about issues related to tobacco, disease prevention, and health promotion Our successes include such projects as banning smoking on domestic airline flights, revising warning labels on cigarette packages and advertising, and obtaining warning labels on smokeless tobacco products. On the state level, the Coalition has also succeeded in limiting exposure to environmental tobacco smoke indoors and limiting youth access to tobacco in several states.

Tobacco use continues to be a major public health problem in the this country and remains the leading cause of preventable death. Tobacco kills an estimated 419,000 Americans each year. Environmental tobacco smoke causes an estimated 3,000 lung cancer deaths each year. An additional 37,000–40,000 cardiovascular disease related deaths can be attributed to passive smoke exposures.

The Coalition on Smoking OR Health believes strong steps should be taken to discourage tobacco use by all segments of our population, including youth, women, and minorities who increasingly are targeted by the tobacco industry. The Coalition also seeks to protect the nonsmoker, adult and child, from environmental tobacco smoke-the primary focus of today's hearing.

The Coalition commends the Senate Environment and Public Works Subcommittee on Clean Air and Nuclear Regulation for its review of the impact of environmental tobacco smoke on human health. We hope today's hearing marks the initial step in your consideration and approval of public policy initiatives—such as the Smokefree Environment Act (S. 1680) and legislation to ban smoking in federal buildings (ILR.881/S.262)—that will not only provide Americans additional protection from the dangers of environmental tobacco smoke, but improve the quality of the air we breathe indoors.

I will begin my testimony with a review of the previous findings on environmental tobacco smoke, or passive smoking, and health effects in nonsmokers to illustrate the development of a growing consensus on the dangers of exposure over time. I will also focus on the EPA conclusions about tobacco smoke exposure and address the reliability of the approach which was used. Lastly, I will bring to the Subcommittee's attention evidence previously excluded from legislative discussions on the effects of environmental tobacco smoke exposures on the development of cardiovascular diseases. The Coalition strongly believes this correlation is worthy of the Subcommittee's review and critical to your deliberations on the impact of passive smoke on human health.

Historical Review of Passive Smoke

The health effects of passive smoking were first reviewed 20 years ago in the 1972 report of the Surgeon General on Smoking and Heals The report concluded that:

> "an atmosphere contaminated with tobacco smoke can contribute to the discomfort of many individuals."

The 1982 Surgeon General's report again examined passive smoking, this time in the context of smoking and cancer. The Surgeon General found that:

> "although the currently available evidence is not sufficient to conclude that passive smoking causes lung cancer in nonsmokers, the evidence does raise concern about a possible serious public health problem"

In 1986 the Surgeon General released a report devoted entirely to the health effects of passive smoking. The Surgeon General concluded that passive smoking is a cause of lung cancer in healthy nonsmokers. In addition, the report concluded that children whose parents smoke have an increased frequency of respiratory infections and respiratory symptoms compared with children whose parents do not smoke. The National Academy of Sciences also issued a report in 1986 that offered similar conclusions.

A third report in 1986 by the prestigious International Agency for Research on Cancer concluded that

> "Knowledge of the nature of sidestream and mainstream smoke, of materials absorbed during "passive smoking', and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens leads to the conclusion that passive smoking gives rise to some risk of cancer."

These reports were developed and edited by different procedures strengthening the validity of the common conclusions.

Finally, in 1991, the National Institute for Occupational Safety and Health published its *Current Intelligence Bulletin no. 54*. "Environmental Tobacco Smoke in the Workplace". NIOSH concluded that ETS is a potential occupational carcinogen-the most significant category for human carcinogens used by the agency.

Respiratory Health Effects of Passive Smoking

The Environmental Protection Agency's risk assessment—supported earlier findings with regard to the risks of lung cancel As you can see, medical and public health communities reached an overall consensus regarding the link between environmental tobacco smoke and serious disease long before the Agency's risk assessment's release on January 7, 1993. In fact, given the mounting evidence on the dangers of passive exposure in recent years, the fundamental question following this consensus remains—"Why did it take the EPA so long to initiate and complete its risk assessment."

For record, the EPA risk assessment found that, in adults:

- Environmental tobacco smoke causes an estimated 3,000 lung cancer deaths and was classified as a class A carcinogen.
- Environmental tobacco smoke exposure leads to coughing, chest discomfort, and reduced lung function in nonsmoking adults.
- The risk assessment also found that over 70 percent of lung cancer deaths attributable to passive smoke exposures are due to exposures outside of the home.

The EPA risk assessment also augmented previous reports with an exhaustive review of the health effects of environmental tobacco smoke on children Although the tobacco industry has repeatedly tried to refute the findings of this risk assessment as they pertain to the lung cancer risks for adults, the results concerning respiratory disease in children have not received such attention.

For the record, I would like to review briefly the findings regarding the risks for children when they are eased to environmental tobacco smoke:

- 8,000 to 26,000 cases of childhood asthma per year are attributable to environmental tobacco smoke;
- Symptoms of 200,000 to 1 million children already diagnosed with asthma become significantly worse due to environmental tobacco smoke exposures;
- 150,000 to 300,000 cases annually of lower respiratory tract illness in young children under 18 months are attributable to environmental tobacco smoke;
- 7,500 to 15,000 hospitalizations in these younger children result from exposure to environmental tobacco smoke; 15,000 hospitalizations for lower respiratory tract illness would equate to between $45 million and $68 million annually, given the average cost per patient with such a diagnosis.

Reliability of Science

As one might expect, the tobacco industry continues to make numerous attempts to divert attention from the EPA's findings, arguing, mainly, the methodological approach used by the Environmental Protection Agency to reach its conclusion is a portrayal of "poor" science. Need I remind the Subcommittee this is the same industry that still questions whether direct active smoking kills, even in light of the more than 50,000 studies that demonstrate this fact.

The tobacco industry has constructed its campaign of controversy and themes of poor science with questions about statistical significance, meta-analysis, confidence intervals, use of the Agency's cancer guidelines, etc. The industry, in making its criticisms, implies capricious and irresponsible behavior on the part of the Agency's scientific and administrative staff.

However, it must be noted that all decisions regarding the development of the risk assessment were made in conjunction with and agreed upon by an independent body of scientists, the Agency's Scientific Advisory Board, Indoor Air Quality and Total Human Exposure Committee. In fact, Members of Congress and the scientific community were highly criticized early in the developmental phase of the risk assessment as biased toward the tobacco industry.

The tobacco industry's campaign of controversy regarding the EPA risk assessment parallels the attacks it has leveled at the Surgeon General's Reports on Smoking and Health since the initial report was published in 1964. Given the tobacco industry's continuing campaign of deception and denial, it is instructive to quote from the preface to the 1979 Surgeon General's Report on Smoking and Health, written by former Secretary of Health, Education and Welfare, Joseph A. Califano, Jr.:

> "In truth, the attack upon the scientific and medical evidence about smoking is little more than an attack upon the science itself: an attack upon the epidemiological, clinical, and experimental research disciplines upon which these conclusions are based. Like every attack upon science by vested interests, from Aristotle's day to Galileo's to our own, these attacks collapse of their own weight."

For the record, I wish to submit testimony presented before the House Agriculture Subcommittee on Specialty Crops and Natural Resources by Douglas W. Dockery, Associate Professor of Environmental Epidemiology at the Harvard School of Public Health. Dr. Dockery concludes his remarks in this statement with comments which best characterize the Coalition's assessment of the EPA report and industry assertions:

> ". . . .the epidemiologic evidence for an association between lung cancer and environmental tobacco smoke is compelling. The EPA report is a comprehensive, rigorous, balanced, and scholarly summation of the current state of the science which supports such a finding.'

In addition to Dr. Dockery's comments, I wish to comment on the misinterpretation of results and findings of several studies by the tobacco industry. The industry has continued to misuse these studies to further its claims of "poor" science. [Dr. Dockery's statement appears immediately following Dr. Taylor's statement.]

The Tobacco Institute, in materials distributed at the time of the release of the final risk assessment, argues that recently published studies on environmental tobacco smoke, including one of the largest studies to date and funded by the National Cancer Institute, reported no statistically significant increase in risks The Tobacco Institute also asserts that the Agency chose not to include such studies in the risk assessment because their conclusions would have changed dramatically.

Among the more recent studies cited by the industry is the Brownson study, Passive Smoking and Lung Cancer in Nonsmoking Women". (*Am. J. Public Health*, 82:1525–30, 1992.) In reality, the Environmental Protection Agency excluded the Brownson study as well as three other positive studies regarding environmental tobacco smoke and lung cancer because they were published after the cut-off date for literature inclusion. The Agency had been under pressure from Congress and the medical community to complete the risk assessment.

While the Brownson study found that the overall risk based on the spousal smoking exposure surrogate is not increased, it did find that the risk in the highest exposure group shows a statistically significant increase. Brownson's own conclusions state:

> "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking. Comprehensive actions to limit smoking in public places and worksites are well-advised."

Similarly, the Stockwell study, "Environmental Tobacco Smoke and Lung Cancer in Nonsmoking Women," was also not included in the EPA risk assessment The tobacco industry claims this to be a negative study and therefore left out purposefully. However, the author states:

> "In conclusion, the results described here suggest that long term exposure to environmental tobacco smoke increases the risk of lung cancer in women who are nonsmokers. Risks appeared most elevated for non-adenocarcinoma lung cancers. High levels of exposure during youth and adulthood may each play a role in increasing lung cancer rise" (*Journal of the National Cancer Institute, 84:1417–22, 1992.)*

Inclusion of such studies would, if anything, have strengthened the conclusions of the Agency's risk assessment.

Passive Smoke and Cardiovascular Diseases

I wish to turn the Subcommittee's attention to the impact of passive smoking on cardiovascular diseases and death previously not reviewed as a part of the EPA's risk assessment I will begin by presenting the facts regarding cardiovascular diseases and passive smoke exposure and conclude with a review of the studies that led us to this conclusion.

In 1977, the American Heart Association published their first assessment of the effects of cigarette smoking on producing cardiovascular diseases. Since this assessment, numerous published studies have validated original assessments on the adverse health effects of active cigarette smoking. It is now accepted, for example, that over 400,000 deaths occur each year due to active cigarette smoking, and that 200,000 of these deaths are due to cardiovascular diseases.

Each year in this country nearly one million deaths occur because of heart disease while cancer claims an additional 500,000 lives. In addition, this year as many as 15 million Americans will have a heart attack, and about one third of them will die. Of those with coronary heart disease, over 50 percent are male and 48 percent are female. Over 3 million people in the United States have angina, or more commonly know as chest pain. An estimated 350,000 new cases of angina occur each year. The major causative factor responsible for these heart attacks is the formation of atherosclerotic plaques in the blood vessels, or hardening of the arteries—a typical physical change often seen over time in persons exposed to passive smoke.

Cigarette smoke contains many harmful substances, but I wish to only discuss a few. The effects of nicotine, carbon monoxide, and environmental tobacco smoke on the development of cardiovascular diseases are substances to mention here, since they can often lead to stroke and heart attack.

When these substances are present in human lungs after exposures to passive smoke, studies have shown that endothelial plaques (or blood clots) will form and coronary blood vessel blockage will occur. As time progresses, heart attacks will result This is especially true in subjects with pre-existing heart problems. Nicotine, for example, causes increased heart rate and higher blood pressure in humans. In turn' these reactions force the heart muscle to work harder, increasing the heart's blood flow. Tobacco smoke also activates the circulating white blood cells and tissue macrophages within the immune system, altering the shape of cells lining the blood vessels (or the endothelial cells).

Environmental tobacco smoke causes platelets to adhere to the walls of the blood vessels. The probability of this reaction is higher when the Mood vessel walls are damaged. Platelets can clog vessels and lead to the formation of blood clots. clots occlude, or obstruct heart blood vessels, especially if they have become weaker.

Finally, carbon monoxide reduces the ability of the red cells to carry oxygen to the tissues and decreases the onset of angina in exercising heart patients. Active cigarette smoking, by producing these adverse effects on the heart and circulation, is known to produce the formation of atherosclerotic plaques. If unabated, the process continues causing the plaques to block blood vessels carrying nutrients and oxygen to the heart muscle. If untreated, the heart muscles can be severely damaged and death will ensue.

Several studies conducted in both animals and human models now indicate that cigarette smoke causes the above effects. This is especially true in regard to the activation of lymphocytes and tissue macrophages, which are vital to the human immune system and release substances which damage the cells that line the blood vessels.

Below is a summary of some of the studies reviewed in the paper I authored in *Circulation* 86:69, 1992. This paper was used by the American Heart Association to reach its conclusions regarding the impact of passive smoke on cardiovascular diseases. For the record, I would like to submit a copy of this report and ask that it appear in its entirety in the hearing record.

In 1991, Drs. Stanton Glantz and William Parmley published an assessment (*Circulation* 83:1, 1991) of cardiovascular related deaths associated with environmental or passive cigarette smoke. They assessed ten published studies using death as the endpoint for nonsmokers living with smokers. All studies (except one) had a risk factor greater than one (1 = no risk) and the overall risk factor was 13. Glantz used this data to calculate a pooled relative risk of 13 for men (95 percent confidence interval of 1.1—1.6) and 12 for women (95 percent confidence interval of 1.2—1A) to predict 37,000 cardiovascular deaths in the U.S. caused by passive cigarette smoke.

In January 1992, Dr. Kyle Steenland (*JAMA* 267:95, 1992) analyzed nine epidemiologic studies with risk factors varying from 0.9 to 3.0. Assuming that the observed cardiovascular risk is due to environmental tobacco smoke exposure, Steenland predicted that 35,000–40,000 schemic heart disease (low blood flow) deaths occurred each year due to this factor. In addition, he also analyzed the data from 5 studies to include former smokers living with smokers, of which 3 studies were controlled for cardiovascular risk actors (cholesterol, high blood pressure, obesity).

To summarize:

First, approximately twice the number of heart related deaths occur as compared to lung cancers in the population of *active* cigarette smokers (200,000/100,000).

Second, the EPA report on the effects of environmental tobacco smoke on producing lung cancer is a very scientific and scholarly study which has withstood many negative analyses by the tobacco industry. The EPA studies predicted that 3,000 lung cancer deaths occur each year due to passive tobacco smoke after carefully evaluating over 30 studies involving subjects who were nonsmokers living with smokers.

Third, using these statistics and epidemiological studies and the fact that cardiovascular deaths result in twice the number of diseases in people who smoke as those who develop lung cancer, it is not a great leap of faith to predict that at a minimum 6,000–8,000 cardiovascular deaths occur each year due to passive smoke.

Fourth, in the American Heart Association paper we also predicted 35,000–40,000 cardiovascular deaths per year caused by environmental smoke and the data are very convincing. In fact, the data collected in the 1970s and 1980s predict similar numbers of deaths although different data and assumptions were used in epidemiological studies.

Although some question the usefulness of meta-analysis, it is the best approach we now have to analyze data concerning environmental tobacco smoke and cardiovascular diseases. Like any measure of effect, the approach must be done with care which was certainly done in the studies used in the analysis quoted. Dr. John Tukey, a very famous statistician once said, and I fully agree with this statement, "Science does not begin with a tidy question, nor does it end with a tidy answer." [Olkin, I. *The Sciences* July/August, p. 30, 1992.]

Fifth, the recommendations in the American Heart Association position paper were 1) to ban smoking in public places, and 2) to enhance public awareness of the dangers of environmental tobacco smoke at work, but also at home—after all, children are so innocently exposed to environmental tobacco smoke in the homes of smokers.

The American Heart Association, the American Lung Association, and the American Cancer Society all support conclusions of the American Heart Association position paper. I applaud the Members of Congress who are taking a positive stance on this important health issue to impose a ban on smoking in all federally owned buildings and a ban in all public places.

Based on a number of public opinion surveys conducted by the Gallup Organization for the American Lung Association, it is clear that more and more Americans believe environmental tobacco smoke is harmful. Many polls also have indicated the public prefers smokefree public places, as opposed to those in which smoking, though restricted, is permitted.

In the most recent survey, conducted in 1992, 9 in 10 adults were aware that environmental tobacco smoke is harmful to infants and young children, pregnant women, and older healthy adults. Women were more likely than men to believe that environmental tobacco smoke is harmful to all of these groups. Nonsmokers also were more likely than smokers to strongly agree about the harmful effects of environmental tobacco smoke. An important finding was that even 8 in 10 smokers know that environmental tobacco smoke is bad for the people around them.

Conclusion

From the evidence the Coalition on Smoking OR Health has presented to you today, it is clear that more and more Americans understand that environmental tobacco smoke is harmful. Given the accepted consensus in the medical, scientific, and public health communities about the risks of environmental tobacco smoke and the growing public awareness of these risks, we would do this nation greater service by moving forward with legislation to protect the public from the dangers of environmental tobacco smoke. We urge this Subcommittee to take the steps necessary to spur full Senate consideration and passage of public policy needed to adequately address the issue of exposure. Please know that the Coalition is ready to offer any assistance that it can throughout the legislative process.

Thank you.

[Note: Additional attachments to this statement have been retained in committee files.]

HARVARD SCHOOL OF PUBLIC HEALTH
Department of Environmental Health
Environmental Epidemiology Program

Procedural and scientific issues relating to the environmental tobacco smoke report released by the EPA on January 7, 1993. Hearing of the Subcommittee on Specialty Crops and Natural Resources. July 21, 1993

Prepared testimony by Douglas W. Dockery, Associate Professor of Environmental Epidemiology

Thank you for the invitation to testify on the scientific issues surrounding the environmental tobacco smoke report[1] released by the EPA on January 7, 1993. In the invitation letter, Mr. Rose suggested that the Subcommittee would consider issues relating to the risk assessment procedures, including: application of the Agency's Carcinogen Classification Guidelines to data on ETS; EPA's evaluation of the ETS data, including its use of the meta-analysis technique, its selection of particular epidemiologic studies to include in its analysis, and the statistical methodololgy employed; and other EPA risk assessment projects, including how the relevant data bases compare with those for ETS. Let me discuss each of these issues separately.

Criteria for Classifying ETS as a Carcinogen

Tobacco smoke is a known cause of lung cancer. The carcinogenicity of tobacco smoke has been demonstrated by all methods used to assess risk – that is, in animal bioassay studies, genotoxicity studies, and epidemiologic studies. Moreover, tobacco smoke is a strong carcinogen. Epidemiologic studies have shown that active-smokers develop lung cancer at a rate at least ten times that of never-smokers. Epidemiologic studies have shown that the risk of lung cancer associated with tobacco smoke increases with exposure, measured either by number of cigarettes smoked per day, or years of cigarette smoking. There is no evidence from these studies of active smokers that there the smallest exposures to active smoking are free of risk. It follows immediately that exposures to low concentrations of tobacco smoke should be associated with increased risk of lung cancer. **The evidence that tobacco smoke is such a strong cause of lung cancer, without any other consideration, is sufficient to define environmental tobacco smoke as a lung-cancer hazard.**

There is also substantial evidence showing that nonsmokers are passively exposed to tobacco smoke at nontrivial levels. That nonsmokers are breathing environmental tobacco smoke, and are therefore at risk of developing the same diseases as active-smokers, is a fact so clear that it should require no further discussion. Nevertheless, a considerable mass of data has been developed estimating environmental exposures to tobacco smoke, direct measurements of ambient indoor concentrations of tobacco smoke, and direct measures of dose based on biologic tissue samples. The evidence that large numbers of people in the general population are exposed

to this carcinogen is sufficient to define environmental tobacco smoke as a lung-cancer hazard.

Given that tobacco smoke is associated with increased incidence of lung cancer even to the lowest exposures among active-smokers, and that there is widespread environmental exposure to tobacco smoke among nonsmokers, increased incidence of lung cancer should be expected among never-smokers chronically exposed to environmental tobacco smoke. Indeed, increased incidence of lung cancer has been consistently observed in studies of never-smokers exposed to environmental tobacco smoke. Moreover, we also should expect to observe increased incidence of other cancers associated with active tobacco smoking among never-smokers environmentally exposed to tobacco smoke. **Evidence from epidemiologic studies that never-smoking women with smoking spouses have increased risk of lung cancer only confirms what was apparent from the carcinogenicity of tobacco smoke itself.**

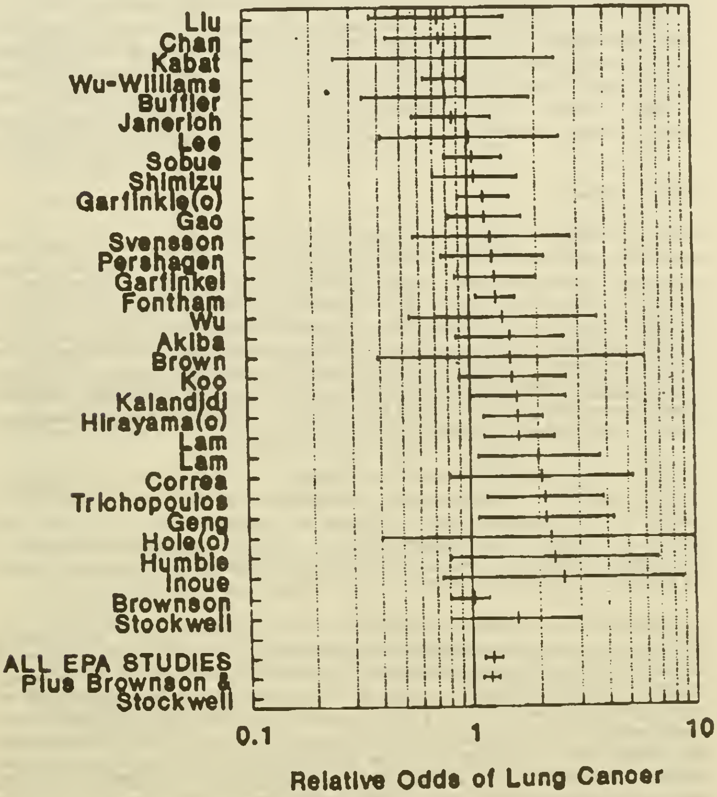
Use of Meta-Analysis

Given the compelling evidence cited above, the hypothesis to be tested is not that tobacco smoke has no statistically signficant association with lung cancer in epidemiologic studies. Rather, the hypothesis to be tested is that environmental tobacco smoke does not increase lung cancer risk. Of the 30 studies reviewed by the EPA[1], only one study[2] was not consistent with an increased lung-cancer risk associated with spouse smoking. The consistency of these results across so many independent studies showing a positive association between lung cancer and spousal smoking is a very strong statement of the robustness of those findings. In epidemiologic studies of effects of environmental hazards, such consistency and robustness is a much more important indicator of causality than statistical significance.

The attached figure presents my summary of the available epidemiology data showing the association of lung cancer in non-smoking women with the cigarette smoking of their husbands. Results from the 30 studies considered by the EPA plus two studies which appeared subsequent to the writing of the EPA report, are presented. For each study, the estimated relative odds of lung cancer associated with husband's cigarette smoking is presented along with the 95% Confidence Inerval for that estimate. A relative odds greater than one (that is, on the righthand side of the plot) indicates that lung cancer in these non-smoking women is positively associated with their husbands' smoking. It is clear from this plot that almost all of these studies have found such a positive association.

Critics have suggested that these associations may be the result of bias or counfounding in the data -- that is, that the observed associations are due to some characteristic other than spouse smoking which is related to both lung cancer and spouse smoking. While each study has its weakness, and bias and confounding must be considered in any study, it is my interpretation of these studies that bias and confounding have generally acted to underestimate the true association between lung cancer and environmental tobacco smoke exposure. Other design issues -- such as the fact that spouse smoking is only a crude measure of environmental tobacco smoke exposure in the home, at work, and in other settings -- will also produce underestimates of the true association.

EPIDEMIOLOGIC STUDIES OF HUSBAND'S SMOKING & LUNG CANCER



Critics have also suggested that the use of meta-analysis techniques, as in the EPA Report, are inappropriate for epidemiologic data. In this I strongly disagree. Meta-analysis is a well-developed technique for contrasting and combining results from different studies. Its concepts and methods are actually a simple extension of statistical analysis already used in epidemiology. These methods are commonly used in public health research, particularly in the evaluation of clinical trials[3]. Meta-analysis has been applied in epidemiologic research for many decades[4] and has recently been the subject of two scholarly reviews[5,6]. The use of these methods by the EPA is not only appropriate but is a significant advance in evaluating the scientific literature.

Meta-analysis is significant because it provides an objective method for combining data and for evaluating effects estimates from different studies. Moreover, it provides a method for contrasting various studies in the literature and for evaluating the effects of bias, confounding, and other issues of importance in epidemiological studies. For these reasons, I think that the EPA analysis, following similar meta-analyses of ETS and lung cancer by the National Academy of Sciences[7] and the U. S. Surgeon General[8], has been most responsible in applying this technique to an environmental agent. I strongly support the use of meta-analysis in rule-making.

Selection of Studies

As far as I can tell, the EPA report included all studies available at the time of writing. With the continual publication of new studies showing the adverse effects of environmental tobacco smoke, there comes some point, largely determined by forces outside the control of the reviewers, when the writing stops. The EPA Report was published in December 1992. The study by Brownson et al.[9] appeared in the November-1992 issue of the American Journal of Public Health (which means it arrived in my office in late November or early December). The Stockwell et al paper[10] appeared in the September-1992 issue of the Journal of the National Cancer Institute. Given these publication dates, one can hardly suggest that these papers were ignored because they may have "affected EPA's results." Moreover, inclusion of these papers would not have affected the meta-analysis (to be discussed later).

Attached is a copy of my own simple meta-analysis of the original EPA data, taking the weighted mean of the studies as presented in Table 5-5 of the EPA report. The combined estimate over all the studies based on the crude data presented gives me an overall effect estimate of 1.24 (with a 95% confidence internal of 1.13 - 1.35). Including the Brownson[9] and the Stockwell[10] studies in that analysis (as shown in the attached table) only minimally changes the overall effect estimate to 1.21 (with a 95% confidence interval of 1.11 - 1.31).

If a decision were to be based on a single study, I consider the Fontham et al[11] study to be the best study, and certainly the statistically most powerful study, conducted so far. Its power is indicated by the weights given to this study in my attached meta-analysis. It has the strength of being a prospective study -- looking at 420 incident primary lung cancers that are pathologically confirmed -- with very good exposure estimates and very good definition of the health outcomes. The Brownson[9] study is also a large study, having 432 lifetime non-smokers, and also has a high weight given to it in the meta-analysis. The weakness of this study is the relatively poor exposure data, as compared to the Fontham study. Nevertheless, a positive association was found between spouse smoking and lung cancer which increased with years of

Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects.

Summary of Epidemiologic Studies of Risk Based on Exposure Assessed by Spouse Smoking Habits When Available, or Smoking by Household Cohabitants. Data from Table 5-5 (US EPA,1992).

Authors	Year	OR	90% CI Lower	Upper	Var (lnOR)	Weights	ln(OR)* Weight
CASE-CONTROL STUDIES							
Akiba et al.	1986	1.52	0.96	2.41	0.078	12.79	5.36
Brownson et al	1987	1.52	0.49	4.79	0.480	2.08	0.87
Buffler et al.	1984	0.81	0.39	1.66	0.194	5.16	-1.09
Chan and Fung	1982	0.75	0.48	1.18	0.076	13.13	-3.78
Correa et al.	1983	2.07	0.94	4.52	0.228	4.39	3.19
Fontham et al	1991	1.32	1.08	1.61	0.015	67.90	18.85
Gao et al	1987	1.19	0.87	1.63	0.036	27.46	4.78
Garfinkel et al.	1985	1.31	0.93	1.85	0.044	22.88	6.18
Geng et al	1988	2.16	1.21	3.84	0.123	8.12	6.25
Humble et al.	1987	2.34	0.96	5.69	0.293	3.42	2.91
Inoue & Hirayama	1988	2.55	0.9	7.2	0.399	2.50	2.34
Janerich et al.	1990	0.86	0.57	1.29	0.062	16.23	-2.45
Kabat and Wynder	1984	0.79	0.30	2.04	0.339	2.95	-0.69
Kalandidi et al. *	1991	1.62	0.99	2.66	0.063	15.85	7.65
Koo et al.	1987	1.55	0.98	2.44	0.077	13.01	5.70
Lam	1985	2.51	1.49	4.23	0.101	9.94	9.15
Lam et al.	1987	1.65	1.22	2.22	0.033	30.20	15.12
Lee et al.	1986	1.03	0.46	2.20	0.214	4.67	0.14
Liu et al.	1991	0.74	0.37	1.48	0.178	5.63	-1.70
Pershagen et al. *	1987	1.28	0.82	1.98	0.051	19.77	4.88
Shimizu et al.	1988	1.08	0.7	1.68	0.071	14.12	1.09
Sobue	199C	1.06	0.79	1.44	0.033	30.03	1.75
Svensson et al.	1989	1.26	0.65	2.48	0.166	6.04	1.40
Trichopoulos et al.	1983	2.08	1.31	3.29	0.078	12.76	9.35
Wu et al. *	1985	1.41	0.63	3.15	0.169	5.93	2.04
Wu-Williams, Samet	1990	0.79	0.64	0.98	0.017	59.62	-14.06
Brownson et al *	1992	1.03	0.80	1.20	0.011	93.47	2.76
Stockwell et al. *	1992	1.60	0.80	3.00	0.114	8.80	4.13
COHORT STUDIES							
Butler *	1988	2.02	0.48	8.56	0.540	1.85	1.30
Garfinkel *	1981	1.17	0.85	1.61	0.027	37.66	5.91
Hirayama	1984	1.38	1.03	1.87	0.033	30.43	9.80
Hole et al. *	1989	2.27	0.4	12.7	0.778	1.29	1.05

	ORmh	95% CI Lower	Upper	Var (lnOR)	Weights	
Overall for						
Case-Control Studies	1.23	1.11	1.36	0.205	416.57	85.22
With Brownson and Stockwell Studies	1.19	1.10	1.30	0.178	518.84	92.12
Overall for						
Cohort Studies	1.29	1.02	1.63	0.254	71.23	18.07
Overall for						
Studies in EPA Report	1.24	1.13	1.35	0.212	487.80	103.29
With Brownson and Stockwell Studies	1.21	1.11	1.31	0.187	590.07	110.19

* 95% Confidence Intervals reported

exposure. The authors conclude: "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking." This certainly is consistent with all the evidence that has been presented in the other studies.

Statistical Methodology

The tobacco interests have questioned the use of 90% Confidence Intervals in the meta-analysis. The Confidence Interval reflects only one of several elements that must be considered in the evaluation of epidemiologic studies: the Confidence Interval is a quantitative measure of the statistical or random error in the data and reflects, therefore, only the influence of chance in these data. It is inappropriate to define an adverse health effect by a statistical significance or a Confidence Interval; therefore, whether that definition is based on a 90% Confidence Interval or a 95% Confidence Interval is irrelevant.

Use of a 90% (rather than 95%) Confidence Interval in this case corresponds to use of a one-tailed (rather than two-tailed) test of statistical significance at the $p=0.05$ level. In the case of a known carcinogenic agent, such as tobacco smoke, it is entirely appropriate to use a one-tailed or one-sided test of significance for an adverse effect of tobacco smoke. We would not expect tobacco smoke to be a protective agent against cancer and therefore the use of a 5% one-tailed test, or equivalently a 90% Confidence Interval, is justified.

Other Risk Assessment

The tobacco interests have compared EPA's risk assessment of environmental tobacco smoke (ETS) with risk assessments of electromagnetic radiation (EMF) and of chlorinated water. First, an important difference betwwen ETS and these other environmental exposures is that there is little or no supporting evidence for the EMF hypothesis available in the literature at the moment. The meta-analysis is only one component of a multi-factorial evaluation that has to be undertaken in classifying an agent as a carcinogen. While evidence for a positive association may be found for EMF, there is a lack of evidence for strong occupational effect or evidence of other effects at high-EMF exposures as is shown for direct tobacco smoke. Secondly, there is a lack of the strong toxicologic basis that has been developed for tobacco smoke.

Tobacco smoke has been shown to be a carcinogen in laboratory experiments; tobacco smoke has been shown to be a carcinogen in studies of humans actively smoking themselves, and, in multiple studies, environmental tobacco smoke has been shown to be an environmental carcinogen. There is not the same body of evidence for EMF or chlorinated water suggesting that there are effects demonstrated in laboratory experiments or at very high exposures and, until such a body of evidence is developed, it would be inappropriate to move forward with a similar finding for those particular agents.

In my opinion, the epidemiologic evidence for an association between lung cancer and environmental tobacco smoke is compelling. The EPA Report is a comprehensive, rigorous, balanced, and scholarly summation of the current state of the science which supports such a finding. While epidemiologic studies alone cannot demonstrate causality, the universal finding of the carcinogenicity of tobacco smoke in animal and genotoxicity studies corroborates the epidemiology. There is no doubt that tobacco smoke is an environmental carcinogen.

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American College of Physicians
American Public Health Association
American Society of Internal Medicine
Association of State and Territorial Health Officials
March of Dimes Birth Defects Foundation
National Coalition of Hispanic Health and Human Services Organizations (COSSMHO)
Society of Cardiovascular & Interventional Radiology

June 7, 1994

Honorable Joseph I. Lieberman
Chairman
Subcommittee on Clean Air and Nuclear Regulation
U.S. Senate
Washington, D.C. 20510

Dear Sen. Lieberman:

Enclosed please find the responses to questions for the record which you and Sen. Faircloth requested from Dr. Aubrey E. Taylor. Dr. Taylor testified on May 11, 1994 on behalf of the American Cancer Society, American Heart Association, and American Lung Association, united as the Coalition on Smoking OR Health.

Questions similar to the ones raised at your subcommittee hearing were also asked of another Coalition on Smoking OR Health witness at a House hearing last year. I am enclosing a copy of those questions and responses with a request that these also be included in the hearing record.

Sincerely,

Fran Du Melle
Steering Committee
Coalition on Smoking OR Health
Deputy Managing Director
American Lung Association

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RESPONSES BY DR. AUBREY E. TAYLOR TO ADDITIONAL QUESTIONS FROM SENATORS LIEBERMAN AND FAIRCLOTH

ADDITIONAL QUESTIONS FROM SENATOR LIEBERMAN

Question 1. You have testified that between 35,000 and 40,000 cardiovascular deaths each year are attributable to passive smoke exposures. Dr. Jane Gravelle has testified that a more accurate estimate of ETS-related cardiovascular deaths in nonsmokers, based on a physical extrapolation method, is 700 deaths and perhaps only 3 if the dose-response relationship is non-linear. What is your opinion of Dr. Gravelle's estimate of ETS-related deaths? Do you believe that the physical extrapolation method produces a more accurate estimate of nonsmoker ETS exposures than an epidemiologic method? If no, why not?

Answer. Dr. Gravelle's estimates of ETS-related deaths due to cardiovascular disease use a physical extrapolation method and therefore underestimate the number of deaths. The Gravelle estimate uses cigarette equivalents to arrive at this risk factor, a method most epidemiologists have soundly rejected as an appropriate measure of exposure. For example, Gravelle uses "cotinine, a biomarker for nicotine to determine cigarette-equivalents. This is fundamentally flawed because nicotine is removed from the air very quickly (nicotine has a propensity to adhere to rugs and walls). If a different marker of exposure were used, such as exposure to particulates, a completely different result would occur. The 1986 Surgeon General's report on the health consequences of involuntary smoking found that, depending on the marker used, estimates of nonsmoker exposure to cigarette-equivalents have ranged from 1/100th of a cigarette per day to 25 cigarettes per day—a difference of more than 3 orders of magnitude.

Steenland evaluated the cardiovascular data using the 5 best designed studies with largest groups (7 year follow-up—1245 men married to smokers; 12 year follow-up—4162 men, 14,873 women living with smokers or ex-smokers; 12 year follow-up 3960 men, 4037 women living with smokers or ex-smokers; 20 year follow-up—513 women living with smokers; in 1960, 16 year follow-up—91,540 women married to smokers or ex-smokers). He predicted that 35,000–40,000 ischemic heart disease deaths occurred due to ETS. These were all cohort studies (nonsmokers living with a spouse who smokes), of which three were controlled for major cardiovascular risk factors (cholesterol, blood pressure and obesity). Three showed a positive dose response while the other two showed a dose response in certain subgroups.

There are limitations to any statistical methodology. However, in my opinion, there is sufficient data available to enable the American Heart Association to predict that 35,000–40,000 deaths occur each year in the United States due to environmental tobacco smoke exposure. It is critical to note the common risk factor among all subjects was ETS and that people living with smokers or ex-smokers have a greater incidence of CVD and lung cancer than nonsmokers living with nonsmokers.

Question 2. Dr. Gravelle has argued that the overall increased risk of 30 percent for heart disease, which your analyses attributes to exposure to ETS, is implausible since the increased risk of heart disease from active smoking is only 70 percent to 90 percent. How do you counter this criticism?

Answer. The relative risk for *active smoking* is 1.7, while most studies of *never smokers living with smokers* show risk factors of 1.2–1.3 as compared to populations of *never smokers* living with *never smokers*. What could cause the relative risks of ETS to be higher than one would expect?

Epidemiological studies on *active* smokers have used reference groups of never smokers composed of never smokers not exposed to ETS and never smokers exposed to ETS. Therefore, relative risks of mainstream and passive smoking are not comparable since the control populations are different.

Dosimetry based on cigarette equivalents is misleading since sidestream smoke is qualitatively different from mainstream smoke and is considered by many to be more toxic than mainstream smoke. Please note that Dr. Coggins said emphatically at the subcommittee hearing that the exposure to ETS was equivalent to about 1½ cigarettes per year. He has since changed his calculation showing how imprecise cigarette equivalents are in predicting exposure.

Several experimental studies and epidemiologic studies strengthen the case for a true association of ETS and heart disease. The comparisons are simple: observed relative risk for never smokers exposed to ETS to those not exposed. This risk analyses estimates the annual number of deaths due to ETS exposure among never smokers in the USA and provides excellent and useful insight into the public health burden of ETS.

Question 3. EPA Administrator Carol Browner has testified that there are only two ways to effectively protect nonsmokers from involuntary exposure to ETS: (1) banning smoking indoors and (2) restricting smoking to separately ventilated rooms. Do you agree with Administrator Browner that these two options are the only methods that effectively protect nonsmokers from involuntary exposure to ETS? If so, why?

Answer. Banning smoking indoors will decrease ETS exposure in the work place and public buildings. Unfortunately current regulations and proposals will not impact exposure in the home. Education on an ongoing basis will be needed to reduce the large numbers of parents smoking in the presence of children. Restricting smoking to separately ventilated rooms can decrease BTS exposure of smokers, but does not provide the same level of protection to nonsmokers unless the ventilation completely eliminates the tobacco smoke, i.e., no smoke or its products linger in the room. Well ventilated rooms can reduce ETS in the work place provided that nonsmokers do not have to enter the smoking room.

ADDITIONAL QUESTIONS FROM SENATOR FAIRCLOTH

Question 1. Are you familiar with the methodology used in A. Judson Wells' 1988 paper? If so, can you address the scientific validity of his work?

Answer. If one reads Wells' paper, it appears as though he basically formulated two estimates and "picked" a value simply because it was halfway between an unadjusted and adjusted estimate. On what basis can such an unscientific approach be used as a basis for legislative action?

Question 2. You also mentioned a recent review article by Steenland. Do you know how he arrived at his conclusions? What scientific justification can you provide to take, as he did, 1960s data from a single state (Maryland) and apply it to the entire U.S. population and assume that its risk estimate would be relevant some 30 years later?

Answer. Wells estimated that 32,000 heart disease deaths among nonsmokers were attributable to ETS. Wells included all former smokers in the population at risk for ETS heart disease and he extrapolated American society data from 1960 for heart disease rates to the 80s. Surprisingly, Steenland (who analyzed never smokers ischemic heart disease death rates from cohort studies in the 1970s and 1980s) and Wells (who used a different means to estimate the prevalence and effect of ETS exposure for heart disease) found similar risk factors, although the studies used different basic associations and assumptions. Steenland's use of the Maryland data is close to the present estimations and does not affect his risk factor calculations.

Question 3. How many known risk factors are there for heart disease? Can you name the already identified risk factors?

Question 4. Are you aware of any data which provide support for the theory that there may be important differences in the presence of certain risk factors in smokers vs. nonsmokers and in smoking households vs. nonsmoking households?

Question 5. You spoke about the number of heart disease deaths "attributable" to ETS and about the interest of the public health. Wouldn't it be relevant to the public health to elucidate what factors are truly related to heart disease risk?

Answer. There are many known heart disease risk factors—the most common ones are smoking, cholesterol, blood pressure, exercise (or lack of) and obesity, and ETS is also a definite cardiovascular risk factor. The combined studies on ETS predict that nonsmokers who live with smokers have a greater risk of having lung cancer and cardiovascular disease than nonsmokers living with nonsmokers, period. When this is coupled with the fact that 400,000 more cardiovascular deaths occur in smokers than in nonsmokers, the results are not surprising.

Some risk factors could be providing protective effects (antioxidants), and others could add to the effect; but the one common factor present in all ETS studies is that people (spouses) living with smokers have a higher incidence of cardiovascular disease than people living with nonsmokers. Also, several studies have corrected for major risk factors and still predict similar relative risks for environmental tobacco smoke. ETS is the major risk factor when all studies are considered.

Question 6. You said that the EPA's risk assessment on ETS was "one of the most scholarly pieces of scientific work" you have seen. Yet you stated that you are not an epidemiologist and wish you knew more about epidemiology. Your qualifications to scientifically grade the EPA report (which is a review of epidemiological studies), not those of an experienced statistician or epidemiologist. . correct?

Question7. How do you justify the EPA's change of the confidence intervals midway through the process?

Answer. Senator, I have been a scientist for 34 years, published over 600 papers, abstracts, and 5 books, all of which contain some type of statistical analyses. In fact, I have been continuously funded for 34 years to do cardiopulmonary research and have been the Editor of several scientific journals, and I have received numerous awards for this research. In all these capacities, I have had to analyze data in a critical fashion. I find the EPA report on ETS and lung cancer a superb study that presents risk assessments, their strengths and weaknesses and the statistical power of each study. This is excellent epidemiological science. Even when the data is analyzed under a microscope, the studies still predict 3,000 lung cancer deaths each year in the nonsmoking U.S. population attributable to ETS. Since active tobacco smokers produce twice the number of cardiovascular deaths as compared to lung cancer then a simple estimate predicts 6,000–7,000 cardiovascular deaths must occur each year from ETS. However, when well designed heart disease studies have been carefully analyzed for nonsmokers living with smokers, the risk factor prediction is much higher, since they predict 35,000–40,000 deaths a year occur in the nonsmoking U.S. population due to ETS.

I have discussed with colleagues the so-called problem with the EPA analyses—the one-tailed analyses. If the data is defined normally, then 2.5 percent of the population should be found on the two ends of a normal curve. What was done in the EPA lung cancer analyses (but not in several other grouped analyses in that report) is that a 5 percent one-tailed test was used. It is not uncommon to only look at the positive effect of something in a population, rather than both ends of the distribution curve, but the 90 percent confidence interval must be used when evaluating one tail of the curve.

Finally, no epidemiological study should be taken out of context relative to the overall risk factor that is being evaluated—smoking. There is absolutely no doubt that smoking kills 400,000 people each year in the USA. ETS contains many compounds that cause heart disease by placing the heart muscle at risk: nicotine, carbon monoxide, and substances which alter platelets and neutrophil function—these compounds and many others contained in smoke can cause pathological conditions that accumulate over several years to cause arteriosclerosis and cardiovascular damage. The data is simply overwhelming that ETS kills 40,000 Americans each year. Importantly, there is absolutely no need for this health hazard to continue to cause heart disease in people who do not smoke. All this needless nitpicking won't change the outcome of the lung cancer and heart disease deaths occurring in this country in people exposed to smoke in the home, work place, and public buildings; when any careful and proper analyses of the available data is performed—ETS is a dangerous health hazard and should be eliminated from our society.

TO PROHIBIT SMOKING IN FEDERAL BUILDINGS

(103–16)

HEARINGS

BEFORE THE

SUBCOMMITTEE ON
PUBLIC BUILDINGS AND GROUNDS

OF THE

COMMITTEE ON
PUBLIC WORKS AND TRANSPORTATION
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRD CONGRESS

FIRST SESSION

ON

H.R. 881

TO PROHIBIT SMOKING IN FEDERAL BUILDINGS

MARCH 11; APRIL 22, 1993

Printed for the use of the
Committee on Public Works and Transportation

U.S. GOVERNMENT PRINTING OFFICE
70–453 WASHINGTON : 1993

HARVARD SCHOOL OF PUBLIC HEALTH,
Boston, MA, July 19, 1993.

SUSAN F. BRITA,
Staff Director, Subcommittee on Public Buildings & Grounds, House of Representatives, Washington, DC.

DEAR MS. BRITA: Following my testimony before the subcommittee on April 22, 1993, I received two sets of questions from Representative Valentine. I am enclosing a copy of those questions plus my response. I trust you will find this material useful and will distribute it as appropriate.

Sincerely yours,

DOUGLAS W. DOCKERY,
Associate Professor, Environmental Epidemiology.

HEARING ON H.R. 881—QUESTIONS FROM REPRESENTATIVE VALENTINE

ON EPA'S USE OF A 90 PERCENT CONFIDENCE INTERVAL

1. Q: Do you agree with EPA that it was appropriate to switch from 95 percent to 90 percent confidence intervals in the ETS report, even though 95 percent is the universally accepted scientific standard?

A: Use of a 90% (rather than 95%) confidence interval in this case corresponds to use of a one-tailed (rather than two-tailed) test of statistical significance at the p=0.05 level. In the case of a known carcinogenic agent, such as tobacco smoke, it is entirely appropriate to use a one-tailed or one-sided test of significance for an adverse effect of tobacco smoke. We would not expect tobacco smoke to be a protective agent against cancer and therefore the use of a 5% one-tailed test, or equivalently a 90% confidence interval, is justified.

2. Q: I'm told that in the great majority of the individual studies EPA evaluated, in the first draft of the ETS risk assessment and in virtually all other EPA risk assessments, the Agency has relied upon 95 percent confidence intervals. Yet in the final draft of the ETS assessment, EPA had switched to a 90 percent confidence interval. And, as we discover, the studies considered in that final draft didn't produce a statistically significant result at the 95 percent level. Is it your view that all of that is simply confidence?

A: The confidence interval reflects only one of several elements that must be considered in the evaluation of epidemiologic studies. The confidence interval is a quantitative measure of the statistical or random error in the data and reflects, therefore, only the influence of chance in these data. It is inappropriate to define an adverse health effect based on a statistical significance or a confidence interval, and therefore whether this is based on the 90% confidence level or the 95% confidence level is irrelevant.

3. Q: You've done a considerable amount of original research yourself, I believe. Have you ever reported your results in terms of 90 percent confidence intervals? If not, why not, and if so, what was the basis for your decision?

A: The purpose of the confidence interval is to estimate the statistical variance, that is, the confidence in the effect being estimated. Causality is not determined by crossing an arbitrary statistical line. Statistical significance is only one of many criteria that must be used in evaluating cause and effect. In many cases we have reported harmful or beneficial effects which do not achieve statistical significance based either on a 5% two-tailed or on a 5% one-tailed test, that is, on bounding the so-called no-effect estimate, or null hypothesis.

ON META ANALYSIS

4. Q: EPA considered 11 U.S. studies in its meta analysis of the ETS data. I am told that not one of those 11 studies originally reported a statistically significant overall increase in risk at the 95 percent confidence level. Only by combining the studies, adjusting the data and lowering the standard of confidence could EPA claim that the result was statistically significant. Do you consider it valid to take 11 studies which show nothing individually and artificially combine them to produce a significant result?

A: Meta-analysis is a significant innovation in the review of scientific literature. It provides an objective method for combining data and evaluating the effects estimates from various studies. Moreover, it provides a method for contrasting various studies that are in the literature and for evaluating the effects of bias, confounding, and other important issues in epidemiological studies. In this sense, I think that the EPA analysis, in following similar meta-analyses of ETS and lung cancer by the National Academy of Sciences[1] and the U.S. Surgeon General,[2] has been very responsible in applying this technique to an environmental agent. I strongly support the use of meta-analysis in rule-making.

5. Q: Do you think 11 studies which essentially show nothing are an adequate basis for a Group A classification?

A: I disagree with your assertion that these studies show nothing. While most of these studies fail to achieve statistical significance, they are universally consistent with a positive association between environmental tobacco smoke and increased risk of lung cancer. Therefore bringing these studies together in the meta-analysis is an appropriate evaluation of their strengths. But these studies have to be evaluated based on other potential sources of error, confounding, and bias, as well as random error which is measured by the confidence interval. I think the EPA has done an excellent job in evaluating these alternative explanations, both in the meta-analysis and in their qualitative review.

ON EPA'S OMISSION OF DATA

6. Q: You may or may not know that several months before EPA released the final version of the ETS risk assessment, a very large ETS study was published in the American Journal of Public Health. This study, sponsored in part by the National Cancer Institute, is the largest study of its kind ever conducted in the U.S. and, I'm told, is of a design similar to the other studies EPA considered.

As I understand it, when that study and another recent U.S. study are added to EPA's meta analysis, the resulting risk estimate is not statistically significant even if the lower 90 percent confidence interval is applied.

Do you think it was appropriate for EPA to simply ignore this study even though it is quite large and clearly relevant to EPA's analysis, just because it would have affected EPA's result?

A: When a document such as the EPA report is being prepared, there is obviously some cutoff date at which the work and the editing stop and the document goes to publication. With new studies coming out continually showing the adverse effects of environmental tobacco smoke, there comes some point, largely determined by forces outside the control of the reviewers, when the writing has to stop. The EPA report has a publication date of December 1992. The study by Brownson et al.[3] in the November-1992 issue of the American Journal of Public Health (which means it arrived in my office in late November or early December). The Stockwell et al paper[4] appeared in the September issue of the Journal of the National Cancer Institute. Given the dates, one can hardly suggest that these papers were ignored because they may have "affected EPA's results." Moreover, as discussed later, inclusion of these papers would not affect the meta-analysis.

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[1] National Research Council. (1986) Environmental tobacco smoke: Measuring exposures and assessing health effects. Washington, DC: National Academy Press.

[2] U.S. Department of Health and Human Services. (1986) The health consequences of involuntary smoking. A report of the Surgeon General. DHHS Pub. No. (PHS) 87–8398. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

[3] Brownson RC, et al. (1992) Passive; smoking and lung cancer. American Journal of Public Health 82: 1525–1530.

ON THE EPA GUIDELINES FOR CARCINOGEN ASSESSMENT

7. Q: I am told that even EPA's Science Advisory Board acknowledged that ETS could not be classified as a Group A carcinogen based on EPA's guidelines for Carcinogen Assessment. I understand that the ETS assessment diverges from the guidelines in several respects. First, EPA classified ETS as a Group A carcinogen based primarily on its similarity to active smoking, which is the first time in EPA history that a subsection has been so classified based on the claim that it looks kind of like another substance. Second, the risk estimate in the EPA report is quite small, and because there are no actual data on exposure, it is difficult to rule out the possibility that something else accounts for the observed risk.

And yet, the SAB dismissed the fact that the ETS fails to meet the Agency's guidelines, suggesting that if ETS could not be classified as Group A according to the guidelines, then the guidelines—and not the ETS conclusions—need to be changed.

Does it disturb you at all, as a scientist, that EPA very blatantly changed the rules that have governed all of its other scientific enterprises just in the case of ETS?

A: I was not part of the EPA Science Advisory Board deliberations and therefore cannot comment on their reasoning. I agree with and endorse their conclusions. You suggest that ETS has been classified as a Group A carcinogen based on its similarity to active smoking. I would agree with such a line of reasoning. The same chemical agents, including many known carcinogens, which are found in main-stream tobacco smoke are also seen in side-stream tobacco smoke, sometimes at higher concentrations. Based solely on the presence of these carcinogens in side-stream tobacco smoke, I think it is appropriate to classify environmental tobacco smoke as a carcinogen. We have many similar examples, such as coke-oven emissions and asbestos, where effects have been demonstrated in occupational or high-exposure areas and which have led to regulation of those same emissions as environmental carcinogens. Secondly, you suggest that the risk is small, or at least compared to the risk from active smoking. But that does not mean it is not important. In fact, compared to the relative effect that would be expected, given the quantification of exposure from environmental tobacco smoke compared to active tobacco smoke, the effect is much larger that one would expect if the effect were scaled by the relative exposures. Moreover, because of the large number of people exposed, the risks of cancer from ETS imply many more incident cancers than would be expected from coke-oven emissions, absestos, or other Class A carcinogens. Therefore, I hardly consider this a change in the rules and find it consistent with previous practice.

8. Q: What other substances can you identify for which it would be appropriate to change the rules if the rules don't produce the result you want?

A: As described above, this rule-making has followed the same rules which have generally been applied and I do not accept your suggestion that rules have been changed for environmental tobacco smoke.

9. Q: If EPA's guidelines for Carcinogen Risk Assessment shouldn't be relied upon to produce the Agency's risk assessments, then what rules should govern the risk assessment process? Should all federal agencies simply abandon risk assessment principles, and do whatever seems to make the most sense to them?

A: This evaluation of the effects of environmental tobacco smoke has brought a high degree of quantification and scientific rigor to the field of risk assessment which in the past was based on individual evaluations of epidemiologic and toxicologic studies. The combining of data in the meta-analysis and the quantitative and rigorous evaluation that is applied has set an important precedent for future studies.

ON THE PRECEDENTS SET BY THE ETS RISK ASSESSMENT

10. Q: You may or may not be aware of comparisons that have been made between the strength of the data on ETS and the strength of the data on electromagnetic radiation (EMF), for example, and chlorinated water. According to my information, there are more individual studies in the case of EMF—40 for EMF as opposed to 30 or so for ETS—and they generally report higher relative risks. Yet

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[4] Stockwell HG, et al. (1992) Environmental tobacco smoke and lung cancer risk in nonsmoking women. Journal of the National Cancer Institute 84: 1417–1422.

EPA called the results for EMF "far from conclusive." Similarly, I'm told that scientists who have evaluated the data on chlorinated water say the relative risks are stronger than for ETS.

If EPA conducted a meta analysis on the data for these substances, applied a 90 percent confidence interval and produced a statistically significant result, would you agree that they should be classified as Group A carcinogens?

A: The important difference is that there is little or no supporting evidence for the EMF hypothesis available in the literature at the moment. The meta-analysis is only one component of a multi-factorial evaluation that has to be undertaken in classifying an agent as a carcinogen. While evidence for a positive association may be found for EMF, there is a lack of evidence for strong occupational effect or evidence of other effects at high-EMF exposures as is shown for direct tobacco smoke. And secondly, there is a lack of strong toxicologic basis that has been developed for tobacco smoke.

11. Q: Why do you think EPA finds the ETS data so much easier to interpret than it finds the data for EMF or chlorinated water?

A: Tobacco smoke has been shown to be a carcinogen in laboratory experiments; tobacco smoke has been shown to be a carcinogen in studies of humans actively smoking themselves, and, in multiple studies, environmental tobacco smoke has been shown to be an environmental carcinogen. The difference for EMF or chlorinated water is that there is not the same body of evidence suggesting that there are effects being demonstrated in laboratory experiments or at very high exposures, and until such a body of evidence is developed, then it would be inappropriate to move forward with a similar finding for those particular agents.

12. Q: Assume, for example, that EPA found that the smoke produced by burning wood in your fireplace was similar to coke-oven emissions, which EPA believes to be a Group A carcinogen, in terms of their physical and chemical make up. Would you think that would be reason enough to label diesel exhaust a Group A carcinogen?

Then do you agree with the statement in the ETS risk assessment that the similarity between ETS and active smoking are enough to justify a Group A ranking for ETS even without any further studies?

A: The question is not whether these chemicals are similar for the same specific carcinogenic chemicals are present in main-stream and side-stream smoke. When people are exposed environmentally to the chemical species that has been shown in the laboratory or occupational settings to be carcinogenic, and when epidemiologic studies show increased cancer risk from environmental exposure, then there is clear evidence for a Class A finding. Coke-over emissions have clearly been shown to be strongly carcinogenic among workers; specific agents from coke-oven emission have been demonstrated to be carcinogenic in laboratory experiments. If wood smoke were shown to contain some of those same chemicals, it would raise the question of whether they were carcinogenic. Then the second question that would have to be addressed is whether those effects can be extrapolated to environmental exposures, and it would be the job of the epidemiologists to evaluate those effects in a realistic setting.

13. Q: Are you, as a scientist, comfortable with the principle of basing Group A classifications on similarities between substances? What about basing them on very small risk estimates when you cannot be sure that all important factors have been considered?

A: As implied before, declaring a specific chemical to be a Class A carcinogen should be based, on the combination, first, of evidence from high-exposure evaluations in human populations that there are effects; second of supporting pathologic or physiologic evidence from laboratory experiments, and third, of evidence from epidemiologic studies suggesting that, at characteristic environmental exposures, excess risks can be observed whether or not they are statistically significant.

In the case of environmental tobacco smoke, the evidence is very clear on all three counts. Tobacco smoke has been shown to be a carcinogen among active smokers and we would expect that small risks would also be shown among nonsmokers passively exposed to tobacco smoke. The quantitative risk estimates found in epidemiologic studies are consistent with measured exposures in nonsmokers and provide quantitative evidence for those associations. The EPA document evaluated the important alternative explanations that have been proposed by the tobacco interests and has shown, to my satisfaction, that these cannot explain the observed associations between ETS and lung cancer. There is no evidence in the data to suggest that there are uncontrolled confounders of sufficient magnitude to create the observed associations that have been found in the epidemiologic studies.

ON CREDIBLE SCIENCE, CREDIBLE DECISIONS

14. Q: A panel of scientific experts who were asked by former EPA Administrator Reilly to review the quality of science at EPA issued a report last year entitled Safeguarding the Future; Credible Science Decisions. The report was quite severe in its criticisms of EPA science. To cite just two of the conclusions, the report said EPA science is "of uneven quality" and is "frequently perceived" to be "adjusted to fit policy." That certainly sounds like the quote from the scientist critical of the ETS risk assessment, who said that "The science of which EPA avails itself is that which happens to fit the political agenda of the moment."

Do you agree that EPA tends to exaggerate risks, or "adjust" science, on its preferred policies or on what is politically correct?

A: The EPA review of the health risk associated with ETS is a good example of how risk assessment should be done, using objective criteria for assessing risk and quantitative methods for evaluating the potential for bias and confounding in the epidemiologic studies. This contrasts with the subjective measures which have been used in the past and which are subject to political bias rather than scientific objectivity.

15. Q: How do you view the recent Alar scare, or the apparent exaggeration of dioxin risk, which seem to reflect the same problem at EPA?

A: The EPA analysis of the health effects of tobacco smoke reflects an objection evaluation of a vast array of direct studies—of smokers heavily exposed to smoke, of laboratory experiments, of animal experiments, of epidemiologic studies of the environmentally exposed subjects—all of which point to environmental tobacco smoke as a carcinogen. This vast body of evidence is certainly more compelling than the evidence that was presented in some of the other decisions that have been made by the EPA recently.

QUESTIONS FOR PROFESSOR DOCKERY

1. Q: You were invited by the Subcommittee to give testimony. Please provide the amount and source of any financial support provided to you in connection with your appearance before the Subcommittee.

A: Indeed, I was invited by the Subcommittee to give testimony. I have received no financial support for my time. I have recently been reimbursed by the Coalition On Smoking Or Health for my travel expenses which consisted of economy airline fare, parking for the day at the airport in Boston, and my public transportation costs in Washington, DC. I appreciate your concern for my financial support, and will let you know if I need help.

2. Q: You testified that, according to calculations that you had personally performed, adding the results of two recent ETS studies (i.e., the Brownson and Stockwell studies) to the meta analysis pool used by EPA to derive a relative risk estimate for the U.S. population did not make any real difference. In particular, you said that the combined relative risk estimate remained statistically significant at both the 90% and 95% levels of confidence.

Please provide an explanation of your calculations, showing precisely what data you employed from which studies, as well as any adjustments that you made to the data. Also, if you have not already done so, please calculate the combined relative risk figure for the total number of U.S. studies (i.e., those used by EPA plus Brownson and Stockwell), using exactly the same data components and adjustments that EPA used in its risk assessment.

A: Attached is a copy of the results of my own simple meta-analysis of the original EPA data, taking the weighted mean of the studies as presented in Table 2 of the EPA report. The combined estimate over all the studies based on the crude data presented gives me an overall effect estimate of 1.24 (with a 95% confidence internal of 1.13–1.35). Including the Brownson[3] and the Stockwell[4] studies in that analysis (as shown in the attached table) only minimally changes the overall effect estimate to 1.21 (with a 95% confidence interval of 1.11–1.31).

3. Q: Are you aware of any carcinogen classifications or regulatory actions by any agency of the U.S. government in which a chemical compound was determined to be carcinogenic in humans on the basis of an epidemiologic data base that was statistically non-significant?

A: As stated earlier, statistical significance is not a measure of effect. It is simply a measure of statistical power of study size. The consistency of the epidemiologic studies reviewed in the EPA document showing a positive association between spouse smoking and lung cancer is the most compelling evidence here. The fact that most studies do not attain statistical significance at the 5% level merely indicates that these studies are not large enough to detect the effects or, alternatively, that the crude measure of spouse smoking is not sufficiently precise to provide a statistically significant association.

4. Q: What confidence intervals, 90% or 95%, were reported in the epidemiologic studies reviewed by EPA in its risk assessment?

A: A knowledgeable or even minimally trained statistician or epidemiologist would be able to interpret either the 90% or 95% confidence interval and be able to convert from one to the other with very little effort.

5. Q: What confidence interval was employed in EPA's report of the pooled relative risk estimate in the first draft of its risk assessment in 1990? Did you review either that document or any later drafts at the request of EPA? Please provide a copy of any communications between yourself and EPA staff relating to such reviews. Please highlight any discussion of appropriate statistical methodology, including the choice of the proper confidence interval.

A: All my correspondence with EPA are in the public record. I was not asked to review the lung cancer results nor comment on the statistical methodologies. Nevertheless, I have found the statistical methods applied by EPA to be appropriate and proper.

6. Q: You testified that you disagreed with the assertion that the Brownson study was the largest study of its kind (i.e., a case-control study) conducted in the U.S. Please name any published study or studies that you consider to be larger, and explain your conclusion.

A: I consider the Fontham et al[5] study to be the best study that has been conducted and certainly the statistically most powerful study conducted so far. That is indicated by the weights given to this study in my attached meta-analysis. It has the strength of being a prospective study looking at 420 incident primary lung cancers that are pathologically confirmed with very good exposure estimates and very good definition of the health outcomes. The Brownson study that you refer to is certainly a large study, having a large number of cases (432 lifetime non-smokers). It also has a high weight given to it in the meta-analysis and, as the authors conclude in their study, "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking." This certainly is consistent with all the evidence that has been presented in the other studies.

7. Q: You testified that the similarity between mainstream smoke and ETS justifies the conclusion that ETS is a carcinogen. Are there any other substances that any agency of the U.S. government has determined to be carcinogenic because they are "similar" to some other substance?

A: I would say that this is a very consistent argument, that the same carcinogenic species that are found in mainstream smoke are found in environmental tobacco smoke and this in itself is sufficient evidence for concluding that environmental tobacco smoke is a carcinogen. This has clearly been shown for other substances declared carcinogens (asbestos, benzene, coke oven emissions, for example).

8. Q: In response to questions from Rep. Emerson, Dr. Maurice LeVois submitted a written comment to this Subcommittee on EPA's use of statistics. Please refer to pages 2–4 of his response, in which he quotes from a number of recognized authorities on statistical methodology. It is clear from these authorities, is it not, the EPA departed from accepted practice in its choice of a "one-tailed test" or statistical significance?

A: I'm sorry, I do not have Dr. LeVois's comments available to me, but I certainly do not find anything unacceptable in the use of a one-tailed test of significance in the EPA evaluation. As I've stated before, the tests of significance certainly do not indicate whether there is a health effect or not. The one-tailed test of significance is certainly appropriate here, given that there is no evidence that tobacco smoke should provide a protective effect from lung cancer.

9. Q: You testified before the Subcommittee that you believe there is a misplaced emphasis in scientific research on "a red line" drawn at 95%. Since 1986, you have been listed as primary or co-author of at least 14 research publications of which I am aware in which your results have been expressed as relative risks or odds ratios. In how many of these did you report your results at a confidence level less than 95%?

A: In all of our recent papers, we have reported the confidence intervals of our relative risk or odds ratios in terms of the 95% confidence interval. The important point here is that many of those have bounded the no-effect level of 1, that is, we have not defined effects based on statistical significance (that is, based on a p-value less than 0.5), and some of these are much greater than a p-value of 0.5. But the 95% confidence interval or the 90% confidence interval or any other arbitrary value that one would ascribe to these associations provides an estimate of the confidence that you have in the point estimate.

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[5] Fontham, et al. "Lung cancer in non-smoking women: A multi-center case control study" published (1991) in Cancer Epidemiology: Biomarkers and Prevention (Volume 1, pages 35–43).

ENVIRONMENTAL TOBACCO SMOKE: MEASURING EXPOSURES AND ASSESSING HEALTH EFFECTS—SUMMARY OF EPIDEMIOLOGIC STUDIES OF RISK BASED ON EXPOSURE ASSESSED BY SPOUSE SMOKING HABITS WHEN AVAILABLE, OR SMOKING BY THE HOUSEHOLD COHABITANTS

[Data from Table 5–5 (US EPA, 1992]

Authors	Year	OR	90 percent CI		Var (lnOR)	Weights	ln(OR) Weight[1]
			Lower	Upper			
Case-control studies:							
Akiba et al	1986	1.52	0.96	2.41	0.078	12.78	5.35
Brownson et al	1987	1.52	.49	4.79	.480	2.08	.87
Buffer et al	1984	.81	.39	1.66	.194	5.16	−1.09
Chan and Fung	1982	.75	.48	1.19	.076	13.13	−3.78
Correa et al	1983	2.07	.94	4.52	.228	4.39	3.19
Fontham et al	1991	1.32	1.08	1.61	.015	67.90	18.85
Gao et al	1987	1.19	.87	1.63	.036	27.46	4.78
Garfinkel et al	1985	1.31	.93	1.85	.044	22.88	6.18
Geng et al	1988	2.16	1.21	3.84	.123	8.12	6.25
Humble et al	1987	2.34	.96	5.69	.293	3.42	2.91
Inoue & Hirayama	1988	2.55	.9	7.2	.399	2.50	2.34
Janerich et al	1990	.86	.57	1.29	.062	16.23	−2.45
Kabat and Wynder	1984	.79	.30	2.04	.339	2.95	−.69
Kalandidi et al[1]	1991	1.62	.99	2.65	.063	15.85	7.65
Koo et al	1987	1.55	.98	2.44	.077	13.01	5.70
Lam	1985	2.51	1.49	4.23	.101	9.94	9.15
Lam et al	1987	1.65	1.22	2.22	.033	30.20	15.12
Lee et at	1986	1.03	.48	2.20	.214	4.67	.14
Liu et al	1991	.74	.37	1.48	.178	5.63	−1.70
Pershagen et al[1]	1987	1.28	.82	1.98	.051	19.77	4.88
Shimizu et al	1988	1.08	.7	1.68	.071	14.12	1.09
Sobue	1990	1.06	.79	1.44	.033	30.03	1.75
Svensson et al	1989	1.26	.65	2.48	.166	6.04	1.40
Trichopoulos et al	1983	2.08	1.31	3.29	.078	12.76	9.35
Wu et at.[1]	1985	1.41	.63	3.15	.169	5.93	2.04
Wu-Williams, Samet	1990	.79	.64	.98	.017	59.62	−14.05
Brownson et al[1]	1992	1.03	.80	1.20	.011	93.47	2.76
Stockwell et al[1]	1992	1.60	.80	3.00	.114	8.80	4.13
Cohort studies:							
Butler[1]	1988	2.02	.48	8.56	.540	1.85	1.30
Garfinkel[1]	1981	1.17	.85	1.61	.027	37.66	5.91
Hirayama	1984	1.38	1.03	1.87	.033	30.43	9.80
Hole et al[1]	1989	2.27	.4	12.7	.778	1.29	1.05

	ORmh	95 percent CI		Var (lnOR)	Weights	
		Lower	Upper			
Overall for case-control studies	1.23	1.11	1.35	0.205	416.57	85.22
With Brownson and Stockwell studies	1.19	1.10	1.30	.178	518.84	92.12
Overall for Cohort studies	1.29	1.02	1.63	.254	71.23	18.07
Overall for studies in EPA report	1.24	1.13	1.35	.212	487.80	103.29
With Brownson and Stockwell studies	1.21	1.11	1.31	.187	590.07	110.19

[1] 95 percent confidence intervals reported.

STATEMENT OF DR. JANE G. GRAVELLE, SENIOR SPECIALIST IN ECONOMIC POLICY, CONGRESSIONAL RESEARCH SERVICE

Mr. Chairman and Members of the Committee. We would like to thank you for the invitation to appear before you today to discuss the statistical basis for estimates of the health effects of passive smoking.

Please note that we are trained as economists and our area of expertise relates to economic analysis and the associated areas of statistical inference and quantification of effects for purposes of cost-benefit analysis and related economic policies. We do not have technical expertise in the physiological and biological transmission mechanisms of disease causing agents.

Our involvement in this issue was a result of a research paper we prepared on the proposed cigarette tax. This paper, which is now completed, is entitled Cigarette Taxes to Finance Health Care Reform: An Economic Analysis (CRS Report 94–214 E). In order to assess the economic efficiency of the proposed tax, it was necessary to examine the magnitude of any costs that smokers might impose on nonsmokers; the health effect of passive smoking is one aspect of this cost calculation. This led us to a review of the methodology used to assess the scientific evidence on passive smoking.

Our evaluation of that evidence led to two conclusions: first, the evidence that passive smoking causes disease is far less certain than the effects for active smoking; second, the health costs of these potential passive smoking effects, which we translated into a tax per pack, are likely to be quite small.

The claim that passive smoking results in damage to the health of nonsmokers is based upon both theory and empirical analysis. If the theoretical case for the existence of passive-smoking effects is considered to be sound, it leads investigators to expect to find empirical support for the proposition. This theoretical case can be summarized in three steps: (1) environmental tobacco smoke has many of the same components as smoke inhaled by smokers; (2) there is physical evidence of some absorption by passive smokers of these components; and (3) a positive relationship exists between active smoking and additional disease and health costs, with no threshold observed.

Questions have been raised about this entire chain of reasoning, but the focus in our evaluation is the third link in the chain. This link is based upon evidence on active smokers who report different amounts of smoking. The difficulty with this theory is that even the lightest active smokers experience far greater exposure to and absorption of potential disease-causing agents than do passive smokers. Thus the statistical evidence on active smoking, including evidence of greater damage as smoking increases, is a necessary but not a sufficient condition for establishing a link between passive smoking and health risks. That is, a threshold effect may exist between the lowest levels of active smoking studied and the levels of exposure in passive smoking.

Since the theory is not certain, one approach to studying passive smoking effects is to examine epidemiological ("epi") studies—statistical studies of the incidence of diseases in human populations. Given the small risks that are often found for passive smoking, the statistical problems inherent in epidemiological studies are of far greater concern for passive smoking than for active-smoking studies. That is, when the effects are small, it is more likely that some error in design or specification could be responsible for the results. Given this greater uncertainty, consistency of the results with alternative evidence becomes more critical as a reality check.

An alternative method of estimating passive smoking effects is to extrapolate from active smoking studies based on the relative levels of physical exposure, using some type of biomarker which measures the absorption of substances in the body. This approach, sometimes called the "cigarette-equivalent" approach, suggests a strong possibility that the relationship between passive smoking and disease incidence found in epidemiological studies is larger than expected, and that the statistical problems of the epi studies may be attributing disease incidence to passive smoking that is attributable to other factors. Thus, the combination of the greater statistical uncertainty of passive-smoking epi studies and the potential inconsistency of those results with physical exposure models is responsible for our conclusion that the finding of increased risk from passive smoking is "uncertain."

The remainder of this testimony provides the analysis upon which this conclusion is based. It begins with a discussion of the lung cancer evidence on passive smoking, first discussing the epi evidence. This is followed by a discussion of the physical exposure approach and its potential inconsistency with the epi results. The testimony then turns to a comparison of the epidemiological evidence and physical exposure approach for estimating the risk of heart disease from passive smoking, along with a brief mention of non-lung cancer and respiratory illness in children.

LUNG CANCER

Epidemiological Evidence

A number of epidemiological studies have assessed the effects of environmental tobacco smoke on specific diseases, with the largest body of research focusing on lung cancer among nonsmoking wives of smokers. Based upon these studies, several Government agencies have, in the last few years, taken the position that environmental tobacco smoke causes lung cancer in nonsmoking adults, including the Office of the Surgeon General and the Environmental Protection Agency's (EPA's) 1992 risk assessment that classifies environmental tobacco smoke as a cancer-causing agent.[1] Despite the controversy surrounding this latter report, the estimates of the risk of lung cancer deaths from passive smoking by the EPA are relatively small, amounting to a lifetime risk of death from lung cancer due to passive smoking of from one-tenth to two-tenths of a percent. The positions taken on passive smoking's effects on health by Government agencies and by the EPA 1992 assessment in particular have been subject to criticism by the tobacco industry and by some researchers.[2]

Our discussion draws on the evidence presented on both sides of the passive smoking issue with regard to the statistical and scientific evidence, but pays particular attention to the latest summary of this evidence, the EPA study.[3] The EPA study analyzed and summarized 30 studies of passive smoking lung cancer effects.

(1) Critics have questioned how a passive-smoking effect can be discerned from a group of 30 studies of which six found a statistically significant (but small) effect, 24 found no statistically significant effect, and six of the 24 found a passive smoking effect opposite to the expected relationship.

EPA attempted to standardize this diverse group of studies to account for statistically important differences in their methodologies. In this process, EPA reduced the standard for statistical significance from the usual standard, and the one generally used in the original studies. It is unusual to return to a study after the fact, lower the required significance level, and declare its results to be supportive rather than unsupportive of the effect one's theory suggests should be present, but our conclusion about the "uncertainty" of the EPA results is not dependent upon this change in significance levels.

However, the issue raised by the change in the statistical significance standard should not be ignored. The test of statistical significance used in these studies answers the following question: How large a chance, statistically speaking, is society willing to take that it accepts a conclusion that a passive-smoking effect exists when in fact a passive-smoking effect does not exist? In effect, EPA changed the standard from a two-and-a-half percent chance to a five percent chance of accepting an incorrect conclusion. The implication for policy is that society has accepted a greater chance of focusing resources on an unjustified intervention (from an efficiency standpoint).

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[1] U.S. Department of Health and Human Services, *The Health Consequences of Involuntary Smoking, 1986*, Surgeon General Report, DHHS Publication Number (CDC) 87–8398; and United States Environmental Protection Agency, *Respiratory Health Effects of Passive Smoking: Lung and Other Cancer Disorders*, December 1992.

[2] A group of tobacco growers and manufacturers has filed a lawsuit challenging the EPA assessment as not being supported by the evidence. Among the issues raised is the use of empirical work based upon exposure in the home to draw inferences about health effects from exposure in the workplace.

[3] These sources include the U.S. Department of Health and Human Services, Surgeon General Reports for 1986 and 1989; United States Environmental Protection Agency (1992), which detail the rationales for their positions. These reports also summarize the epidemiological studies on environmental tobacco smoke, especially on lung cancer and childhood respiratory illness. The reader is also referred to a hearing at which researchers who both supported and criticized the EPA study appeared: U.S. Congress, House Committee on Agriculture Subcommittee on Specialty Crops and Natural Resources, *Review of the U.S. Environmental Protection Agency's Tobacco and Smoke Study*, 103rd Congress, 1st Session, July 1993. For a view that questions the passive-smoking hazard, focusing particularly on lung cancer, and that is written for the layman, see Gary L. Huber, Robert E. Brockie and Vijay Mahajan, "Passive Smoking: How Great a Hazard?" *Consumers' Research*, July 1991, 10–15, 33–34. Huber, et al. also wrote a companion paper on cardiovascular disease "Passive Smoking and Your Heart," *Consumers' Research*, April 1992, pp. 13–19, 33–34. Also, see Kyle Steenland, "Passive Smoking and the Risk of Heart Disease," *Journal of the American Medical Association*, January 1, 1992, Vol. 267, pp. 94–99. These last two articles provide capsule summaries of epidemiological studies on passive smoking and heart disease. Finally, see The Tobacco Institute, *EPA Report Scientifically Deficient* for a summary of the industry's criticism of the EPA report. Some critics of the claim that passive smoking causes disease have also raised questions about institutional bias in the Government or in the professional journals; those issues are not addressed here.

(2) One important difference among the studies is the chance of accepting the absence of a passive-smoking effect when in fact a passive-smoking effect exists. The smaller the size of the sample (number of observations, or people, for whom data were available), the greater the chance of making such a mistake. To correct for these differences, EPA adjusted (weighted) the estimate of the passive-smoking effect in each study. This has the effect of reducing the importance of studies with small sample size, studies that would tend to find less significant effects for passive smoking, and increasing the relative importance of studies with large sample size, studies that would tend to find more significant effects for passive smoking.

(3) EPA adjusted the results of each study for misclassification bias (classifying smokers or former smokers as never-smokers). It also made subjective judgments about the extent to which the studies suffered from a variety of other statistical problems, such as confounding (failure to consider the influence of other factors that might increase lung cancer risk). Those that fared poorly in this analysis were placed in a "Tier 4" category and excluded from the analysis of joint significance of the studies. This procedure allowed EPA to "emphasize those studies thought to provide better data . . . ". (EPA, p. 5–61). After making all these adjustments, EPA combined the studies to conclude that, as a group, the remaining studies indicate that exposure to passive smoke produces a statistically significant increase in lung cancer among nonsmokers.

(4) Another test the EPA conducted was to examine the included studies for evidence of a positive relationship, within each study, between risk and degree of exposure (number of years the husband smoked, or number of cigarettes he smoked per day). They found such a relationship in 10 of the 14 studies for which such data were available. They also found that the highest-exposure-level group had higher risks than other groups combined, which was statistically significant in 9 of 16 comparisons. These results increased EPA's confidence in the integrity of the data, making it more willing to draw conclusions. This confidence comes from the fact that these results conformed to expectations. From our perspective, these results also are consistent with expectations about the functional form of the passive-smoking dose/response relationship. We will return to this issue in the section on the physical exposure approach.

(5) In addition, there are several potential statistical problems. These studies do not have (and indeed cannot have) very precise estimates of exposure from environmental tobacco smoke. The data are based on interviews of the subjects or their relatives. If errors in measurement occur in a systematic way that are correlated with development of the disease, the effect would be to bias the results. An example would be if those individuals who developed lung cancer (or relatives of those individuals) remembered or perceived their exposure differently from those who did not develop the disease.

Another concern is the possibility that some subjects classified as nonsmokers are actually current or former smokers and that such current or former smokers are more likely to be married to husbands that smoke. While EPA made some adjustment for this effect, it is not possible to correct precisely for this problem. That is, it remains possible that a relationship observed might reflect the effects of active rather than passive smoking.

In addition, while EPA considered the presence of certain confounding factors in its evaluation of some of the studies, this issue is not laid to rest. If wives of smokers share in associated poor health habits or other factors that could contribute to illness and that are not or cannot be controlled for, statistical associations found between disease and passive smoking could be incidental or misleading. Such an error could also render a relationship between risk and degree of exposure spurious.

In fact, there is evidence, as discussed in our cigarette tax study, that smokers are greater risk takers than nonsmokers and that they tend to engage in many other lifestyle habits that are not favorable to health. If smokers tend to be less concerned in general about health risks and engage in other behaviors (e.g. diet, lack of preventive health care) that might be shared with their spouses, these factors may be responsible for some share of the estimated increased health effects.

Such limitations of studies are often inevitable, but they impart some degree of uncertainty to the results, especially when small risks are estimated.

(6) Two epidemiology studies that each covered a large number of observations were published in 1992 after the cutoff date for inclusion in the EPA report. The one with the largest number of observations found no overall increased risk of lung

cancer among nonsmoking spouses of smokers,[4] the other found an increased, but statistically not significant, lung cancer risk.[5] Both studies looked at exposure levels within their samples and both found a statistically significant increased risk among the highest exposure group in some categories. In smaller exposure groups, the first study found an unexpected negative relationship between passive smoking and disease and the second found a positive, but not a statistically significant, relationship. It has been pointed out that in large studies where the data are broken into several subsets and each is analyzed separately, some associations may be statistically significant as a matter of chance.

Physical Exposure Relationship

An alternative approach to estimating the effects, if any, of passive smoking through statistical studies is through a physical exposure extrapolation approach. We believe a discussion of this approach will shed some light on why one might be concerned about the certainty of the epidemiological estimates. A physical exposure approach was discussed in our cigarette tax paper, and it was also contrasted with the statistical approach in a memorandum prepared by the CRS. We elaborate on those discussions.

As noted earlier, even the lightest smokers studied among active smokers experience far greater exposure to and absorption of tobacco smoke based on common biomarkers than do passive smokers. Therefore, such evidence on active smokers is necessary but not sufficient to conclude that a similar relationship exists for passive smokers. It is entirely plausible that the (unknown) dose/response function rises very little over the range of exposure (dose) levels for passive smokers and begins to rise rapidly as the exposure levels experienced by active smokers are approached.

The existence of an exposure threshold for disease onset below which many passive smokers fall is not implausible. Most organisms have the capacity to cleanse themselves of some level of contaminants. It is for this reason that public policy usually does not insist that every unit of air or water pollution be removed from the environment: the damage of low levels of pollutants is sufficiently small that removal is not cost effective. In fact, strongly nonlinear relationships in which health effects rise with the square of exposure, and more, have been found with respect to active smoking (see Surgeon General's Report, 1989, p. 44). Were these relationships projected backward to construct the lower (unknown) portion of the dose/response function, the observed relationship might lead researchers a priori to expect no empirical relationship.

In fact, the EPA report dismisses linear extrapolation from the active-smoking dose/response relationship to estimate passive smoking effects. Numerous reasons are given for the decision not to make such an inference. The most interesting reason is a suggestion that extrapolation might *underestimate* the response, exactly the opposite of what the discussion above suggested. That is, if the relationship were such that disease rose with the square or more of exposure, or if there were a threshold, a linear extrapolation would overstate the response. The support for this position that linear extrapolation would underestimate the response is based upon a paper by Remmer[6] that suggests small amounts of carcinogenic substances are large enough to begin the disease process but are too small to activate the body's defenses against the disease. In effect, this suggests there is no threshold for disease onset, but there is a threshold for the body's automatic disease fighting mechanisms. Thus, depending upon the relative strengths of the disease and immune responses as dosage increases, marginal disease per unit of dosage could cause the observed average dose/response relationship to increase, decrease, or remain the same as dosage increases for the dosage range that includes passive smoking.

If this is the case, one wonders why EPA's confidence in the epi lung cancer studies was increased by its investigation of the dose/response relationship within the individual studies. Referring back to the discussion in the epi section of this testimony, EPA's theory about a threshold effect for the immune response to exposure should have lead them to expect no particular dose/response relationship.

How do the actual numbers estimated using the different approaches compare? The epi studies indicate an additional risk for lung cancer due to marriage to a smoking spouse for female never-smokers of about 30 percent. That is, according to their analysis of the statistical studies, nonsmoking wives of men who smoke have 30 percent more lung cancer than nonsmoking wives of men who do not smoke. This risk is, in turn, only a tiny fraction of the risk from active smoking (probably around 3 percent)[7]. The risk in the United States epi studies was slightly lower, only about 20 percent. Based on the epi studies' 20 percent risk factors for the U.S., the EPA estimated 3000 lung cancer deaths from passive smoking, 2000 for those who are never-smokers and 1000 for former smokers.[8]

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[4] Ross C. Brownson, Michael C.R. Alavanja, Edward T. Hock, and Timothy S. Loy, "Passive Smoking and Lung Cancer in Women," American Journal of Public Health, November 1992, vol. 82, pp. 1525–1529.

[5] Heather G. Stockwell, Allan L. Goldman, Gary H. Lyman, Charles I. Noss, Adam W. Armstrong, Patricia A. Pinkham. Elizabeth C. Candelora, and Marcia R. Brusa, "Environmental Tobacco Smoke and Lung Cancer Risk in Nonsmoking Women," Journal of the National Cancer Institute, September 16, 1992, vol. 84, pp. 1417–1422.

[6] H. Remmer. Passively Inhaled Tobacco Smoke: A Challenge to Toxicology and Preventive Medicine. Archives of Toxicology, vol. 61, pp. 89–104.

Extrapolation based on physical evidence yields smaller effects. According to data in the EPA report, measures of cotinine in the urine indicate that, overall, passive smokers have about 1/2 of one percent of the level of active smokers. Or, to put it another way, given that the average smoker smokes about 20 cigarettes a day, the passive smoking effect is equivalent to smoking a tenth of a cigarette a day.

In comparing the physical exposure extrapolation approach to the epi estimates, it is simpler to compare the effects on never-smokers. Since the number of current and former smokers are the same as the number of never-smokers, the estimated premature deaths annually from passive smoking for never-smokers would be about 600 using a linear extrapolation.[9] This number is considerably less than the EPA's estimate of 2000 never smoker deaths.[10]

There are potential problems with the physical exposure measure as well as with the epi approach. The physical extrapolation method used above assumes a linear relationship between the incidence of a disease and exposure. Based on evidence from the pattern for active smoking, however, a linear method may not be correct. There is some evidence that disease rises with square of the exposure or even with higher powers in the case of lung cancer.[11] If the disease were to rise with the square of exposure, then the estimate based on cotinine levels would be only 3 people rather than 600 people. Thus, in this case the epi studies suggest 2000 deaths of never smokers and the physical exposure measure suggests 3 deaths and the contrast between the two approaches is even greater.

It is also possible that cotinine is not the best measure of exposure; as discussed in the EPA study some exposure measures show larger and some show smaller effects. It is worth noting that the EPA chose the epidemiological studies as a basis of their approach, but they nevertheless relied on the cotinine measures for several aspects of their estimates (such as extrapolating from the effects on spouses of smokers to the population in general).

Heart Disease and Other Cancer

Many of the statistical concerns raised above with regard to lung cancer are relevant to respiratory effects in children and heart disease in adults. Indeed, the conclusions by these Government agencies about passive smoking and lung cancer are generally not extended to heart disease or other health effects in adults. The presence of other factors that may be related to these illnesses that are not controlled for are particularly important in the case of heart disease, general respiratory illness, and cancers in other parts of the body, where the link between active smoking and the disease is not as strong as in the case of lung cancer.

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[7] The risk of lung cancer in smokers and ex-smokers depends on intensity, duration, and, in the case of ex-smokers, time elapsed since quitting. Passive smoking would involve three percent of the risk of active smoking if there is a ten fold active-smoking risk (i.e. smokers have an additional estimated risk of lung cancer that is ten times the disease rate of nonsmokers) which is typical of current estimates of the risk for women as reported in the 1989 Surgeon General's Report, *Reducing the Health Consequences of Smoking*. U.S. Department of Health and Human Services, DDHS Publication No. (CDC) 89–8411). In generating the estimates of deaths from passive smoking, the EPA actually used the additional risk (of wives married to smokers as compared to wives married to nonsmokers) in the U.S. passive smoking studies, which was about 20 percent. If studies from all countries are considered, the estimated risk from these studies was 30 percent.

[8] Actually, the only number that was directly estimated from the epi study was the calculation of slightly under 500 deaths due to increased risks for women married to nonsmokers. This number was, in fact, extrapolated backward using a linear physical exposure method to calculate an additional 1000 deaths from other sources of environmental exposure (e.g. workplace, social), for a total of 1500 female never-smoker deaths. A further extrapolation yielded 500 additional deaths for male never-smokers, and another 1000 for both male and female former smokers. Lung cancer deaths attributable to passive-smoking are two to three percent as large as the estimated 113,000 lung cancer deaths attributed to active-smoking. For data on widely accepted estimated active smoking deaths, see C. Stephen Redhead, Mortality and Economic Costs Attributable to Smoking and Alcohol Abuse, Congressional Research Service Report 93-SPR, April 20, 1993.

[9] To extrapolate, multiply the ratio of cotinine (.005) by the ratio of never-smokers to ever smokers, and by the 113,000 deaths attributable to active smoking.

[10] There is also a section in the EPA study that discusses extrapolations based on the physical exposure to passive smoking; these estimates also tend to be smaller—in some cases, much smaller—than the epidemiological estimates.

[11] Surgeon General's Report, p. 44.

In addition, the differences between deaths estimated from epi studies and from physical exposure extrapolations are much more pronounced in the case of heart disease estimates.

Recall that the EPA estimate of lung cancer deaths from passive smoking was 3000. There has also been widespread reference to an estimate of 50,000 deaths attributable to passive smoking. The 50,000 estimate has been circulated by non-government organizations, and was mentioned in testimony by the American Medical Association which stated that passive smoking "may kill as many as 53,000" Americans annually.[12] This statement in turn appears to be ultimately traceable to an article by Wells published in 1988 in *Environment International*.[13] This article used existing epidemiological studies to estimate these deaths which included, under one set of calculations, 3,700 lung cancer deaths, 12,300 deaths from other cancers, and 37,400 deaths from heart disease. (Wells actually reported estimates ranging from 38,000 to 53,000, with a preferred estimate of 46,000).[14]

While the estimates from at least some of the epidemiology studies of lung cancer are significantly larger than the estimates based on physical exposure, these results are not magnitudes apart. The same cannot be said, however, for the Wells estimates of deaths from heart disease. Using the same type of linear physical exposure extrapolation as in the previous section would result in 700 deaths from coronary disease for never smokers, and perhaps another 350 for former smokers, with a total of about 1000. The comparable portion of the Wells' 53,000 estimate from the epidemiological studies, even for several years ago, is 37,000, a number that is enormously larger.

This large estimate occurs because the epidemiological studies, on the whole, show a very high risk estimate for passive smoking relative to active smoking for heart disease as compared to lung cancer. For example, Wells indicates a 30 percent additional risk for heart disease for males and a 20 percent rise for females resulting from exposure to passive smoke, as compared to a 70 percent risk for smokers. The passive-smoking deaths associated with these relative risks are immense compared to both the physical exposure extrapolation estimates for heart disease and to either method for lung cancer. Note that although the risk ratios are not that different from lung cancer, the absolute risk estimates are much larger. The risk of lung cancer for nonsmokers is very low, and any percentage of a small number is still a small number. The estimated risk for heart disease is much larger initially, and therefore any significant percentage change in the risk is larger. Put another way, even the epidemiological studies of lung cancer produced passive-smoking deaths of less than 3 percent of active-smoking deaths, while the heart disease studies produced estimates that were 26 percent of estimated active-smoking deaths.

The biological plausibility of passive smoking effects on cardiovascular diseases has been the subject of some discussion.[15] A likely explanation of these apparent large risks from passive smoking found in epidemiological studies for heart disease is, however, the absence of control for other factors.[16] There are many important causes of heart disease (e.g. diet, lack of exercise, lack of preventive health care) that may be engaged in by smokers. There is much evidence that smokers tend to be less concerned about health risks in general. In general, studies do not, and perhaps cannot, control for many of these factors. If smokers' wives share in these behaviors, the relationships found in the epidemiological studies are spurious.

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[12] Statement of the American Medical Association, Health and the Environment Subcommittee, House Committee on Energy and Commerce, Re Adverse Health Effects of Exposure to Environmental Tobacco Smoke, July 21, 1993.

[13] A. Judson Wells, An Estimate of Adult Mortality in the United States from Passive Smoking. *Environment International*. Vol. 14, No. 3, 1988, 249–265.

[14] Each issue of *Environment International* contains an editorial; the one in the issue containing the Wells article was directed at that article. The editorial indicated that the study received mixed reviews from referees (two recommended publication after revision and the third recommended against publication on the grounds that it was too speculative); the editors chose to publish the paper. In the following 3 years there were a series of critiques and rejoinders related to this paper. Letters from Alan W. Katzenstein, Peter M. Lee, and Larry Holcolm criticizing the Wells results; a clarifying letter from Takeshi Hirayama, a rebuttal to Katzenstein and Lee from James L. Repace and Alfred H. Lowrey, and a response from Wells were published in 1990 (Vol. 16, no. 2, pp. 175–193). In 1991, a letter from Stanton A. Glantz criticizing Lee was published along with Lee's reply (Vol. 17, no. 1, pp. 89–91). Later in 1991, a response of Lee to the 1990 letters of Repace and Lowrey, and Wells, a letter from Muin J. Khoury clarifying a point raised in Lee's letter, a joint letter from Glantz and Lee clarifying an issue raised earlier in the year, and a response from Repace and Lowrey, and Wells to Lee's letter were published (Vol. 17, no. 4, 379–387). In 1992 (Vol. 18, No. 3, pp. 315–317, 321–325) another letter from Lee and response from Wells was published.

[15] The argument has been made for a relationship in which passive smoking can have large effects relative to active smoking in some laboratory settings, which is largely attributed to increased sensitivity of some nonsmokers. See Stanton Glantz and William Parmley, Passive Smoking and Heart Disease, in *Circulation*, vol. 53, no. 1, January 1991, pp. 1–12.

The Wells estimate of passive-smoking deaths from cancers other than lung cancer is even larger relative to active-smoking deaths than is the case of heart disease—about 50 percent. Again, these cancers are influenced by many other factors, and the same general criticisms can be made about these epidemiological estimates as in the case of heart disease.

In sum, this analysis suggests that the Wells estimates are so high relative to measures of physical exposure that they seem implausible. It also suggests that the absence of controls or the inability to control for other factors may be a major problem in relying on epidemiological estimates of the health effects of passive smoking. To restate this criticism, if wives or children of smokers share in poor health habits or other factors that could contribute to illness, statistical associations found between disease and passive smoking could be incidental or misleading.

CONCLUSION

Our assessment of the existing evidence on passive smoking was made as a basis for drawing conclusions about the efficiency justifications for an increase in the cigarette tax. Based on that evidence, as indicated in this testimony, our evaluation was that the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking. This finding flows from an analysis of the statistical methodology employed in assessing such health effects and purports to no technical research or conclusion on the physiology of disease-causing agents.

Responses by Dr. Jane G. Gravelle to Additional Questions from Senators Lieberman and Faircloth

QUESTIONS FROM SENATOR LIEBERMAN

Question 1. In the conclusion to your written testimony, you state that, "the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking." You state as the basis for your conclusion that "the evidence that passive smoking causes disease is far less certain than the effects for active smoking. " You also state that your conclusion is based on the "existing evidence on passive smoking.

Are you aware that the existing evidence on ETS and lung cancer includes past studies by the National Research Council, U.S. Surgeons General, the International Agency for Research on Cancer, the Working Group on Passive Smoking, the National Institute for Occupational Safety and Health, conclusions of the American Medical Association and American Heart Association and the Congressional testimony of six Surgeons General? Did you use this evidence in making your conclusion that the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking? If you only looked at the statistical data that EPA used in concluding that ETS is a human lung carcinogen, how can you state that your conclusion was based the "existing evidence" on passive smoking? How do you reconcile your conclusion with the studies that suggests that there is a causal link between ETS and lung cancer?

Answer. The statistical evidence on passive smoking is the epidemiologic studies. For lung cancer, they now consist of slightly over 30 worldwide studies, including 13 U.S. studies (of which the EPA studied 11). There are also studies on a variety of other health effects (heart disease, other types of cancer, respiratory effects). These epidemiologic studies constitute the statistical data source. All of this evidence was considered. Several organizations and individuals have examined and summarized these studies, either on a qualitative basis, or by developing a quantitative risk estimate. Some organizations have simply relied on some other secondary analysis for their positions (e.g., the American Medical Association). These latter are the kinds of studies or testimony mentioned in your question, but they do not provide any new or independent evidence.

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[16] This position is taken by Gary L. Hubert, Robert E. Brockie, and Vijay K. Mahajan in a paper written for the layman: Passive Smoking and Your Heart, Consumers Research, vol. 75., April 1992, pp. 13–19, 32. These authors consider the results in the Wells study and the similar heart diseases study by Steenland (1992) biologically implausible, and also note that six of the nine epidemiological studies show relative risks for passive smokers that are in excess of risks estimated for active smokers and that most have very few controls for the other factors that might affect heart disease.

Question 2. It is my understanding that you tested the validity of EPA's conclusion that ETS is a human lung carcinogen by comparing the epidemiologic results on which it is based with results achieved using a physical extrapolation method. Critics, including the Surgeon General, have indicated that the physical extrapolation method cannot accurately assess non smoker exposure to ETS constituents that may be more harmful than cotinine. How do you justify using the physical extrapolation method as a "reality check" on the EPA analysis given the uncertainty about its inability to accurately assess ETS exposures in nonsmokers? Are you aware of a 1986 Surgeon General report that concluded that the physical extrapolation method is a "complex and potentially meaningless process?" Isn't it possible for this approach to result in a higher "cigarette-equivalent" estimate if different biomarkers for ETS exposure are used?

Answer. Physical extrapolation approaches clearly have shortcomings and there are problems with using this method, including the implicit assumption that there is no threshold. Our estimate used urine cotinine levels, which are about one half of one percent in nonsmokers exposed to passive smoke, but these measures may not represent potential carcinogenic effects. The EPA stresses that there are carcinogens in smoke that may lead to a larger ratio. There are also components that lead to smaller ratio. Some data on active smoking suggests that damage rises faster than exposure in that range of exposure; if this relationship is generally true, linear extrapolation overstates the effects. Of course, if damage rises more slowly than does exposure it would understate effects. Given these uncertainties, physical extrapolation obviously does not represent a precise measure.

Direct statistical estimates also, however, have a number of shortcomings that are likely to persist across all of the epidemiologic studies. Moreover, the numerical estimates from these studies are mid-points in a wide range of expected outcomes (i.e., the confidence intervals around these estimates are large). If both methods are subject to error, and one cannot tell which method is the most flawed, then it would seem to make sense to compare the results. In general, the physical exposure approaches do yield smaller effects. In the case of heart disease these differences are dramatic and, as we indicated in our testimony, suggest that the statistical studies of heart disease may have serious problems.

Please note that the quote referring to the physical extrapolation method as a "complex and potentially meaningless process" in the 1986 Surgeon General's report (p. 200) refers to atmospheric measures and not to biomarkers. We used biomarkers as did the Surgeon General's 1986 report. Another quote from that report: "By using data on nicotine absorption by the nonsmoker, the nonsmoker's risk of developing lung cancer observed in human epidemiologic studies can be compared with the level of risk expected from an extrapolation of the dose-response data for the active smoker." (p. 9). This biomarker approach was also used in the National Research Council's 1986 study (pp. 225–227) to estimate risk.

Question 3. What evidence supports your contention that an exposure threshold may exist for ETS exposures below which no harm from ETS may occur? Do you know of any evidence that has ever suggested that there is not an exposure threshold for ETS? Are you aware that a 1989 Surgeon General report and a 1982 Surgeon General report contained the results of studies that showed linearity in dose response of lung cancer and smoking intensity? If you contend that a threshold level of ETS exposure may exist, what is the exposure level below which no harm occurs?

Answer. The possibility of threshold effect is based on common sense notions, but it is also a standard notion in toxicology and is not denied in the EPA report. (A quote from p. 4–29: "The rapid dilution of both SS and exhaled MS into the environment and changing phase distributions of ETS components over time raise some questions about the carcinogenic potential of ETS under actual environmental exposure conditions.")

Scientists may speculate about the existence of a threshold, and advance biological models with and without a threshold, but they need some sort of empirical evidence to see if it exists. This point is more a matter of logic than of science. If the statement is made that you don't know, a priori, then you don't seek evidence to prove you don't know—you seek evidence to demonstrate an effect.

Also, consider the following quote from the Surgeon General's 1986 Report (after stating that evidence for active smoking shows that cigarette smoke can cause lung cancer): "The question is, rather, can tobacco smoke at a lower dose and through a different mode of exposure cause lung cancer in nonsmokers? The answer must be sought in the coherence and trends of the epidemiologic evidence on this low-dose exposure to a known human carcinogen." (p. 9). Obviously, if it were clear there were no threshold, then there would be no question, and no need for an answer. That is, this statement implies that there may be a threshold.

Question 4. In your written testimony, you state, "EPA changed the standard from a two-and-a-half percent chance to a five percent chance of accepting an incorrect conclusion." What is the basis for your claim that EPA changed the statistical standard? If it is your opinion that EPA's use of a one-tailed statistical test instead of a two-tailed statistical test increased its chance of accepting an incorrect conclusion, don't both tests achieve the same level of statistical significance? Are you aware of the circumstances when use of a one-tailed statistical test instead of a two-tailed test is warranted? If so, do you believe that EPA was warranted in using a one-tailed test to analyze the epidemiologic data on ETS and lung cancer? If no, why?

Answer. The statement that we made in our written testimony (and in our tobacco tax report) that the change in statistical standard is a change from being willing to accept a 2.5 percent chance that there is no true effect to being willing to accept a 5 percent chance that there is no true effect is correct. It doesn't matter why a standard is being changed. The change will still double the chance, whether you describe it as moving from a two-tailed to a one-tailed test, or moving (with a two-tailed test) from a 95 percent to a 90 percent confidence interval. (With a two-tailed, 95 percent test there is a total five percent chance of being outside the confidence interval, with 2.5 percent in each tail; only the one tail is relevant to the chance of no effect, the other is relevant to a larger effect, assuming the estimated relationship is positive. A one-tailed test at 95 percent would have a 5 percent chance in one tail, but it is the same as a two-tailed test at 90 percent, with a total ten percent chance of being outside the confidence interval, and 5 percent in each tail).

In fact, if you examine table 5–9 in the EPA report (pp. 5–28 to 5–29) you will see a reference to a 90 percent confidence interval. (And, if you turn to the discussion of childhood respiratory effects beginning on p. 7–11 you will see constant references to a 95 percent confidence interval, indicating that there was no change for this set of epidemiologic studies.)

There are two issues that are being confused in discussing this issue of the statistical standard. Statistical standards and conventions are always somewhat arbitrary, but we know what they mean in terms of accepting or rejecting a hypothesis. That is the question that we address—your statistical standard determines what chance you are willing to take of accepting an effect when in fact an effect does not exist. Many, perhaps most, people would view a 5 percent change of this type of error acceptable.

There is also a procedural issue, which has concerned some groups and individuals, about the decision to change a statistical standard. These groups believe that there needs to be a uniform standard that would not be varied from one issue to another, in order to minimize political interference in the scientific basis for regulatory decision-making. That point has nothing to do, however, with the technical meaning of the statistical change.

Question 5. In your testimony, you conclude that "the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking." Did you perform any analyses on the data that EPA used to conclude that ETS causes non-cancer respiratory effects in both adults and children. If no, why didn't you consider these possible health effects in your analysis? If yes, please summarize your findings.

Answer. As we indicated, the conclusion about substantial health effects reflects both uncertainty and magnitude. As in the case of lung cancer, the respiratory effects are uncertain because of statistical problems (for example, parents who smoke may be less likely to treat initial symptoms if they tend to be risk-takers in general). There are also fewer studies of each type of effect. As might be expected from our initial focus, we calculated the financial costs, in this case for hospitalizations for children, which were quite small when translated into per pack amounts (one tenth to two-tenths of a cent per pack). Assuming that the costs of treating lower respiratory effects outside the hospital would be small, these aggregate effects would also lead to small per pack amount. Worsening of asthma symptoms is difficult to quantify, but would likely involve a similar magnitude.

Question 6. Do you disagree with EPA's conclusions and analysis concerning ETS's non-cancer respiratory effects on adults and children? Do you believe that ETS causes non-cancer respiratory diseases or other harmful health effects in adults and children? Why or why not? Have you ever estimated the magnitude of non-cancer diseases or other harmful health effects that may be caused by ETS? If so, what were your findings?

Answer. The statistical evidence for respiratory effects is subject to most of the same potential statistical problems as lung cancer (except smoker misclassification in young children), and there may be some additional ones. Although these studies were more likely to control for confounders than did the lung cancer studies, confounders might be a more serious problem in general. Some probably cannot be controlled for. One of the insights that economic analysis of behavior has suggested is that smokers tend to be risk-takers or engage in risky health habits. This finding is consistent with variation in preference functions across individuals—smokers may simply not value health and safety measures as much as nonsmokers and thus spend less effort and money on good health or even a clean environment (and indulge in habits that might harm their health). Consider the ramifications of this view. Individuals who smoke might be less likely on average to engage in preventive health measures for their families, or may be less likely to treat problems when they arise. Or, they may be less concerned about exposure to environmental pollutants in their choice, for example, of where to live. It is also possible that the effects in young children reflect maternal smoking during pregnancy. Therefore, it is possible that when we see more hospitalizations for respiratory problems in children that these problems can be traced to other aspects of behavior (e.g. failure to treat initial symptoms) rather than passive smoking. As we suggested with respect to lung cancer, when the risk ratios are not very large and the studies produce mixed results, as is generally the case with the respiratory studies, the statistical results have some uncertainty.

In our cigarette tax paper, we extrapolated the EPA ratios for lung cancer attributable to passive vs active smoking to other diseases in calculating per pack effects, as well as using physical extrapolation approaches for all diseases. In general, these estimates did not suggest a large per pack cost. The direct epidemiologic studies on heart diseases and cancers outside of lung cancer are subject to much uncertainty because confounding is likely to be more important, and because of the discrepancies between physical extrapolation approaches and statistical effects, as well as the discrepancies (in terms of ratios of passive to active smoking deaths) between these diseases and lung cancer. These are discussed in our written testimony and in the CRS memorandum of March 23 which we supplied to you. As in the case of lung cancer, these statistical studies are characterized by some uncertainty.

QUESTIONS FROM SENATOR LAUTENBERG

Question 1. In your paper on the 75 cent tobacco tax proposed for health care reform, you state the following "An increased cigarette tax as a method of financing health care reform appears questionable on efficiency, budgetary and equity grounds." You draw part of that conclusion from your analysis of the EPA report on environmental tobacco smoke, isn't that correct?

Answer. It is correct that part of our conclusion regarding a cigarette tax reflects our evaluation of the statistical evidence on the health effects of passive smoking, including the information contained in the EPA report.

Question 2. So If you are wrong about the EPA report, wouldn't your analysis of the tobacco tax be skewed?

Answer. A change in the evaluation of the passive smoking evidence would affect our tobacco tax analysis. However, please note that our discussion of the justification of a 75-cent increase in the tobacco tax and our conclusion that a passive smoking effect would not likely justify it rested also on (1) the uncertainty concerning how much passive smoking effects within families should be treated as an external cost that would justify a tax, (2) questions as to whether a tax might harm family members of smokers who continue to smoke after imposition of the tax, clouding the desirability of the tax as a corrective policy for effects that occur within families, and (3) the likely small size of the per-pack correction for passive smoking effects, especially given that there are taxes that are already imposed on smokers.

Question 3. To your knowledge, can you remember a time when a CRS analysis of an issue differed so much from the conclusions of a Federal scientific agency?

Answer. My normal work does not bring me into contact with scientific agencies, but I have had occasion in the past to differ substantially with Federal agencies on economic issues, including those that rested on evaluation of statistical studies of economic behavior.

QUESTIONS FROM SENATOR FAIRCLOTH

Economic Aspects of Legislation

Question 1. It appears as though no one recognizes that there could be important economic ramifications of legislation that is based on an inaccurate interpretation of the data regarding environmental tobacco smoke. Can you briefly highlight some of the economic problems of basing legislation on weak science that suffers from dramatic limitations?

Much sound economic regulation takes place that benefits the consumer, the producers, the investors, and the nation. The economic problems associated with engaging in regulatory action when there is no need for such action include the direct cost of developing and enforcing regulations by the government, and the cost of complying with regulations by businesses. The enforcement costs will be influenced by the degree to which citizens see regulations as fair and appropriate and thus engage in self-enforcement. There are also some indirect costs, principally of interfering in the normal relationships of businesses with their customers and employers and distorting their choices. In some circumstances, even if there are potential health (or nonhealth) effects of a behavior by customers or employees that affect others, economic efficiency may be more likely to be obtained when businesses make private decisions that take into account preferences of all customers and workers, as long as individuals are informed. This approach is most likely to be optimal in a market economy where there are a lot of firms competing for customers and employees and where there is room for diversity. Finally, since many regulations have not been enforced very well, there could be an intangible cost to society, in terms of perceptions of fairness and spillover to other behaviors, when laws are consistently disobeyed.

Question 2. Can you state for us again the reason why "public policy usually does not insist that every unit of air or water pollution be removed from the environment"?

To remove every unit of pollution from the environment would not provide benefits commensurate with costs. The notion of an optimal level of pollution, while it may seem strange, is common in economics. At small levels of pollution, the damage done may be very small or non-existent, but the cost of eliminating the pollution would be very large. For example, the cost of eliminating all automobile emissions would be prohibitive and current standards still allow some pollution levels.

Question 3. Your report suggests, does it not, that the economic savings from environmental tobacco smoke legislation are likely to be quite small? Could the legislation actually be costly?

Our analysis of possible passive smoking effects, translated into a cigarette tax equivalent, appeared to be either absent or small. The effects of regulation of smoking in public places would be smaller, since they only constitute part of any effect. The effects would also depend on enforcement. The cost of the legislation, as noted in question 1 above, would include government and private costs. These costs are hard to quantify. The government budgetary outlay would depend on the enforcement mechanisms. If an attempt is made to monitor compliance and the regulation extends to small as well as larger businesses, the cost would seem likely to be significant. Such calculations are extremely difficult to make, particularly without knowing specific provisions.

Confounding

Question 1. Do you disagree with Administrator Browner's statement that confounding is not an important consideration in the ETS studies?

As indicated in our testimony, we suggest that failure to control for other variables that influence health effects (confounders) could be quite important in studies that find only small risks, as is the case in the passive smoking studies.

Question 2. Can you describe some potential confounders?

For lung cancer, the EPA report lists a number of possible confounders considered in some studies: family history of lung disease, personal history of lung disease, heat source for cooking or heating (combustion by-products), cooking with oil, various dietary factors, and occupation. These factors were not generally controlled for in most of the studies. A recent study sponsored by the National Cancer Institute, not included in the EPA report, found an effect for dietary fat. Other possible risk factors that have been mentioned include exposure to heavy metals, organic chemicals, radon, other natural and man-made radiation, other environmental and occupational pollutants, and emotional and psychological factors.

The list of confounders for general respiratory effects and heart disease is likely to be even longer and confounders more important, since there are many other important contributing causes to these diseases.

Control for some of these effects is sometimes attempted through proxies such as education, socio-economic class, and income level.

Question 3. Can you discuss for us the evidence you mentioned that smokers are greater "risk takers" than nonsmokers? How might this relate to the spousal smoking studies?

In a 1992 study of smokers' risk perceptions, Viscusi discussed research indicating that smokers tend to be risk-takers in the kinds of jobs they take, and there is evidence linking the tendency to smoke to other behaviors (e.g. diet) that may cause health effects. This leads economists to theorize that some smokers may, on average, have less risk aversion, or that they rate health as less important relative to other people. This theory has important implications for the passive smoking studies, because the wives and children of smokers may share in some of those habits which may, in turn, be the cause of the disease. Not only have such confounders often not been included, but, unfortunately, it is probably difficult to measure many of them. And, if they are specific to an individual taste, they cannot be measured by the proxies discussed in the previous question (e.g. education, income class). Thus, these risk-taking attributes increase the uncertainty attached to statistical analyses of the health effects of passive smoking that are based on exposure in the home.

This issue is also important, because the confounding problem could extend across many countries and different cultures (even though the particular types and patterns of habit could vary).

Extrapolation

Question. Can you explain for us why the EPA's claim that extrapolation from active smoking may *underestimate* the potential relationship between exposure to ETS and lung cancer is wrong?

Answer. There are two reasons that linear extrapolation may underestimate the relationship between exposure to ETS and lung cancer: if the measure of relative exposure is incorrect and low relative to the true dosage and if the functional form is super linear (i.e. a doubling of exposure causes less than a doubling of risk). There are three reasons that linear extrapolation may overestimate the relationship: if the measure of relative exposure is incorrect and high relative to the true dosage, if the functional form is sublinear (a doubling of exposure causes more than a doubling of risk), or if there is a threshold.

There is now no way to be certain about these effects. The EPA reviewed studies using linear extrapolation, which tended to produce results below the estimates from the epidemiologic results, although this reflects certain choices made by researchers and does not constitute proof. However, there is, as we suggested, some evidence that the functional form is sublinear among active smokers, with damage rising with the square or more of the exposure (Surgeon General's Report 1989, p. 44). That would suggest that linear extrapolation is more likely to overstate effects, other things equal.

Methodology of the CRS Report

Question. Can you explain for us the method you used to reach your first conclusion that the data on ETS are questionable?

Answer. The main reasons that we suggested that the EPA findings are subject to uncertainty were (1) theory cannot determine a priori that there is an effect because a threshold cannot be ruled out, (2) the statistical studies are subject to several potential statistical problems which could account for the effects given the weak relationships found (potential measurement errors in exposure due to recall bias, possible misclassification of smokers as nonsmokers, and failure to control for other factors, or confounders, that might explain the results) and (3) the subsequent publication of new large U.S. studies that did not generally support the findings, with the largest study finding no effect.

Opinion Regarding EPA Report

Question. Can you elaborate on the deficiencies in the EPA's use of empirical data?

Answer. In answering this question, I will focus on the EPA report itself, rather than the data. There was nothing that the EPA report did that was technically wrong in reporting the studies or in calculating combined effects. The weighting procedure seems reasonable and investigation of a dose-response seems reasonable, although there are always subjective judgments (i.e. should studies be treated equally, what is the confidence interval?). The criticisms are more of interpretation. Here are two or three illustrations. First, the EPA rules out confounders, although, in fact, most of the studies had few controls for confounders. Secondly, misclassification issues are addressed and treated as if they can be dismissed. Nevertheless, there is some uncertainty as to whether the adjustments for misclassification (possibility that some of the individuals who are reported as never smokers are actually former or current smokers, and that the disease relationship may be due to active rather than passive smoking) can really be made. For example, there is really no way to be assured of identifying former smokers, particularly long term former smokers. These are identified by techniques such as discordant answer studies (what percentage of individuals identified themselves as smokers in prior questions) but that approach probably leaves some misclassification in place. Finally, the EPA mentions new studies, but the summary simply quotes from the paper without providing any quantification. Someone reading the report would never know, for example, that the Brownson study was the largest U.S. study ever done but found no overall effect.

STATEMENT OF DR. WILLIAM BLOT, CHIEF, BIOSTATISTICS BRANCH, NATIONAL CANCER INSTITUTE

Good morning, Senator Lieberman and Members of the Subcommittee. My name is William Blot. I am Chief of the Biostatistics Branch of the Division of Cancer Etiology at the National Cancer Institute (NCI). I have been on the staff of NCI for nearly 20 years, conducting epidemiologic research on the environmental and host determinants of cancer. Many of these research studies have evaluated the role of tobacco in cancer risk. I am pleased to be here today to discuss the conclusions of the Environmental Protection Agency's (EPA) Science Advisory Board (SAB) in its review of the EPA Draft Report on Health Effects of Passive Smoking.

In 1990, I was asked to serve as one of about nine consultants to the standing SAB and was requested to address several issues in the Draft Report. Perhaps the most important issue was whether the evidence was sufficient to conclude that environmental tobacco smoke (ETS) is causally related to lung cancer.

The SAB panel met in December 1990 to discuss the Draft Report and review testimony on the health effects of ETS exposure. SAB recommendations were prepared and transmitted to the EPA, and a revised draft incorporating these suggestions and including new information from recently published studies was produced. I received this second draft in the summer of 1992 and was asked to review the EPA's estimates of numbers of lung cancers in the United States that might be due to ETS and to note whether the new data arising since the time of the first Draft Report changed any conclusions regarding ETS and lung cancer. I helped the SAB prepare its recommendations, which were delivered to EPA that fall. The final report, entitled *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*, was issued by EPA early in 1993.

The SAB panel unanimously concluded, based on its review of the totality of available scientific evidence, that the EPA was justified in categorizing ETS as a Class A carcinogen, i.e., a substance that can cause cancer in humans. The SAB also concurred with EPA's assessment that the severity of asthma and the risks of other respiratory diseases in children could be increased from exposure to ETS, but I will restrict my remarks to its association with cancer.

Over 30 epidemiologic studies conducted in the United States and abroad have evaluated risks of lung cancer among nonsmokers exposed to ETS, primarily by studying lung cancer among non-smoking women married to smokers. Not all studies have reported an excess risk linked to ETS, but the great majority have. This consistency and replicability of findings across studies throughout the world establishes that exposure to ETS is indeed associated with a small but measurable increase in lung cancer. Several additional features of the data led the SAB, and me, to conclude that the relationship was likely to be causal in nature, i.e., that it was the ETS that was responsible for the increase in lung cancer among passive smokers. First, virtually all the studies that examined dose-response trends found rising risks of lung cancer with increasing level of ETS exposure. The more the spouse smoked, the greater the risk to the non-smoking partner. This is what would be expected if ETS were a carcinogen. Second, there was no compelling evidence that the association was due simply to bias or confounding by other risk factors for lung cancer. Although only a few studies adjusted for dietary or other risk factors, those that did tended to show little change in the magnitude of the relationship between ETS and lung cancer. Third, increased risks of lung cancer were actually observed at exposure levels found in typical environmental settings. Thus, the risk assessment performed by EPA did not have to rely on extrapolations from high-dose settings as is sometimes done when relevant low-dose data are not available.

Finally, there is the biologic plausibility of the association. ETS arises when people smoke cigarettes. Cigarette smoking is the dominant cause of lung cancer in this country and most others, with upwards of 20-fold excesses of risk in heavy smokers. Nonsmokers exposed to ETS inhale many of the same substances that smokers do, albeit in smaller amounts. Components of tobacco smoke have been detected in the blood and urine of nonsmokers, with some of the carcinogenic compounds in tobacco bound to the hemoglobin of passive smokers. Thus, there is no doubt that tobacco components are absorbed and metabolized by ETS-exposed nonsmokers. There are quantitative differences in the chemical compositions of ETS and inhaled cigarette smoke, but there are a great many qualitative similarities. It is therefore biologically plausible that this lower level of exposure to tobacco smoke from ETS results in an increase in lung cancer risk.

There is uncertainty as to the extent of the increased risk and the exact numbers of cancers among Americans that might result from passive smoking. Such imprecision is a common trait in epidemiologic studies and reflects variations in sample sizes and other characteristics of the available data. Thus, the estimate that 3,000 lung cancer deaths per year in the United States are due to ETS exposure is reasonable, but it is an approximate figure. The SAB recommended that such uncertainty be recognized, but this did not alter our scientific judgment that prolonged exposure to ETS can increase risk of lung cancer. This was the fundamental conclusion drawn by the EPA and also by reviews of the National Academy of Sciences and the Surgeon General several years earlier, and one with which I and the entire SAB fully concurred.

Thank you for this opportunity to testify. I would be happy to answer any questions you may have.

RESPONSES BY DR. WILLIAM BLOT TO ADDITIONAL QUESTIONS BY SENATORS LIEBERMAN AND FAIRCLOTH

QUESTIONS BY SENATOR LIEBERMAN

Question 1. In his written testimony, Dr. Coggins has stated that, "The EPA's approach, much less its conclusions, would not withstand real scientific peer review." In her written testimony, Dr. Gravelle has concluded that, "the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking." As a consultant to the Science Advisory Board which reviewed EPA's report, how do you respond to those statements?

Answer. The EPA report on passive smoking was reviewed by an 18 member panel of scientists with expertise in epidemiology, statistics, toxicology, medicine and other disciplines-relevant to evaluating whether exposure to ETS may cause lung cancer and other respiratory diseases. This relatively large, diverse group conducted a peer review and unanimously endorsed the EPA conclusions that ETS be designated a Class A carcinogen and that exposure to ETS could increase the risk of asthma and other respiratory diseases in children. With respect to Dr. Gravelle's statement, the key may rest upon the interpretation of "substantial". She has estimated that 600 annual lung cancer deaths among never-smokers in the United States may be due to ETS exposure. In her oral testimony she indicated that this number, as well as the EPA's estimate of 2,000 deaths among never-smokers, is only a small proportion of the total of nearly 2,000,000 annual deaths from all causes. Whether 600 or 2,000 is "substantial" is a judgement the subcommittee can review.

Question 2. Did the Science Advisory Board review the methodology contained in the EPA report and, if so, did it find that the methodology used by the EPA was proper?

Answer. The Science Advisory Board found the methodology used in the EPA draft report scientifically appropriate. The Board also recommended that uncertainties in the projections of the numbers of Americans with ETS-related disease be recognized.

Question 3. Do you know of any evidence that suggests that a threshold level for ETS exposure does or does not exist (e.g. there is a level below which ETS exposures do not cause harm)? If so, what is that evidence? If the evidence suggests that a threshold level of ETS exposure does exist, what is that level?

Answer. In my view as a scientist specializing in epidemiologic research on the environmental and host determinates of cancer, there is no compelling epidemiologic evidence that a threshold level exists below which exposure to tobacco smoke (including ETS) is harmless, nor is it likely that such evidence will be forthcoming from existing or ongoing investigations.

Question 4. The tobacco industry has claimed that under EPA's own guidelines for carcinogenic risk assessment, ETS has not met the standard for a Group A carcinogen because the 30 epidemiologic studies contained bias, such as smoker misclassification, and confounding factors. Did the Science Advisory Board discuss the possibility of the presence of bias and confounding factors in the epidemiologic studies when it reviewed the EPA report?

Answer. The Science Advisory Board considered the issues of bias and confounding. The evaluation of bias is difficult, but the method used by EPA to downward adjust the relative risks of lung cancer among ETS-exposed women to account for potential bias was considered reasonable. Confounding by the major cause of lung cancer in the United States, namely cigarette smoking, can be ruled out because the studies focused on nonsmokers. Only a few of the studies assessed confounding by dietary or other risk factors for lung cancer, but those that did found that the positive association between ETS and risk of lung cancer remained after such adjustment.

Question 5. One criticism that has been leveled at the EPA report is that out of the 30 epidemiologic studies it examined, 24 were not statistically significant. If this is true, does it represent a fatal flaw in EPA's conclusion that ETS is a human lung carcinogen? If not, why? Are there other measures of causality, such as consistency, dose response, and specificity? If so, please state whether, using those measures, the 30 epidemiologic studies would show a causal link between ETS exposure in nonsmokers and lung cancer.

Answer. The fact that most of the individual studies did not find a statistically significant overall increase in lung cancer among ETS-exposed nonsmoking women is not a fatal flaw. Most studies did find increases in risk, but because of small sample sizes these increases often were not statistically significant. In combination, however, the investigations provide a consistent pattern: about 80 percent showed an increase in risk and nearly all the studies which examined dose-response trends found rising risks (often statistically significant) of lung cancer with increasing exposure to BTS. Combining these observations with what is known about the hazards of tobacco smoke among smokers, the chemical similarities between ETS and inhaled tobacco smoke, and the detection of tobacco smoke compounds in the blood and other biologic specimens of nonsmokers exposed to ETS, the evidence favors a causal link between ETS exposure and lung cancer.

Question 6. In her written testimony, Dr. Gravelle concluded that, contrary to EPA's estimate of 2,000 never-smoker deaths each year, the estimated premature deaths annually from passive smoking for never-smokers would be about 600 using a physical extrapolation method. She added that if lung cancer were to rise with the square of exposure (e.g. if there is a threshold level for ETS exposure in nonsmokers), the estimate based on a physical extrapolation method would be only 3 deaths. Are you familiar with the physical extrapolation method that Dr. Gravelle used to check the EPA estimate? If you are familiar with this method, what is your opinion regarding its reliability and accuracy? Was Dr. Gravelle's use of the physical extrapolation method scientifically defensible? If no, why? Was Dr. Gravelle's use of the method proper if it is true that lung cancer rises with the square of exposure? If no, why?

Answer. Dr. Gravelle reported that she used a method to estimate how many cigarettes a nonsmoking woman exposed to average levels of ETS would have to smoke to attain the cotinine levels found in the blood of ETS-exposed nonsmokers. The risk of lung cancer associated with this lower level of smoking then would be estimated. Extrapolations are necessary for this estimation because direct observations are unavailable since few smokers smoke less than 5 cigarettes per day. Using a linear extrapolation, Dr. Gravelle estimated there would be about 600 ETS-induced lung cancers annually in never-smokers. This approach has some intuitive appeal, and was considered by the EPA. It results in an estimate lower than that projected by EPA, but could be considered in the same range as the EPA estimate. The problem with this method is that it is not known if out of the several thousand compounds in tobacco smoke cotinine is the appropriate biomarker for estimating risk of lung cancer. Perhaps one of the carcinogens in BTS would be a better marker. With regard to using the square of exposure, there is no direct evidence that risk of lung cancer rises with the square of ETS exposure. Some clues come from studies among smokers, but findings are mixed. In a cohort of 34,000 British physicians, risk of lung cancer has been modelled as being proportional to the square-of-cigarettes smoked per day, but in a cohort of nearly 250,000 U.S. veterans risk rose approximately linearly with number smoked per day.

Question 7. The tobacco industry has claimed that the EPA report did not include two recent studies, Brownson and Stockwell, that were funded by the National Cancer Institute because they did not report a statistically significant increase in lung cancer was associated with ETS exposure. Do you believe that the data contained in these two studies support & refute EPA's conclusions? Please explain why you believe the data either support or refute the EPA's conclusions.

Answer. In combination, the data in the Brownson and Stockwell studies tend to support rather than refute the EPA conclusions (see response to Question 19 submitted by Senator Faircloth).

Question 8. Critics claim that the epidemiologic evidence that the EPA used to conclude that ETS is a human lung carcinogen is weak. As evidence of its weakness, they claim that the risk estimates, which express the statistical correlation for the rate of disease development contained in the epidemiologic data, are low. As a result, they argue that the data does not support EPA's conclusion that ETS is a human lung carcinogen. Did the Science Advisory Board raise this concern when it reviewed the EPA report? Do you concur with the criticism that the evidence that EPA used to conclude that ETS is a human lung carcinogen is weak because of the risk estimates?

Answer. The size of the association between exposure to ETS and risk of lung cancer, as measured by the relative risk of this cancer among nonsmoking women married to smokers, is not large. A relative risk of 1.19 could indeed be called a weak association. This, however, does not mean that the "evidence" is weak. The consistency of findings of excess risk across studies, the nearly uniform detection of dose-response trends, the detection of tobacco smoke components in the bodies of ETS-exposed nonsmokers, and the biologic plausibility, can in fact be considered compelling evidence that ETS is a Class A carcinogen, even though the magnitude of the association is not strong.

Question 9. Dr. Gravelle testified that, based on an assessment of the existing evidence on passive smoking, "the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking." Dr. Gravelle's conclusion is based on her determination that "the evidence that passive smoking causes disease is far less certain that the affects of active smoking." How do you respond to Dr. Gravelle's findings? If her conclusion is true, would the work of many years of the Surgeon General's office in addition to the National Academy of Sciences, the Environmental Protection Agency, the American Medical Association, and the American Heart Association have to be disregarded?

Answer. I have serious concerns about Dr. Gravelle's assessment of the health risks of environmental tobacco smoke (ETS), which disputes well-documented scientific evidence that exposure to ETS is a cause of disease. The medical and scientific evidence that clearly demonstrate a link between smoking and disease also support a link between exposure to ETS and disease. Hundreds of studies, including the 1986 Report of the Surgeon General, *The Health Consequences of Involuntary Smoking*, document the relationship between ETS and health outcomes. The methodology used to develop the Environmental Protection Agency's risk assessment for lung cancer, which classified ETS as a Group A, known human, carcinogen, was rigorous and the literature review comprehensive. Most recently, the largest study to date of women who had never smoked but were exposed to ETS further supported the EPA's risk assessment that long-term exposure to ETS increases the risk of lung cancer in nonsmoking women. As you suggest, the medical and scientific community agree on the health effects of exposure to ETS, and there is no question in my mind that ETS is responsible for approximately 3,000 lung cancer deaths among nonsmokers every year.

The health risks associated with ETS are especially significant for children. Each year ETS causes up to 300,000 lower respiratory tract infections (pneumonia and bronchitis) in children less than one and a half years old, and hospitalizes up to 15,000 of them. Children's exposure to ETS from parental smoking has been causally associated with a number of non-cancer respiratory diseases and disorders including an increased prevalence of respiratory symptoms of irritation (cough, sputum and wheeze), an increased prevalence of middle ear effusion (a sign of middle ear disease), a small but statistically significant" reduction in lung function as tested by objective measures of lung capacity and additional episodes, and increased severity of asthma in children who already have the disease. In addition, epidemiological evidence is suggestive but not-conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms. Finally,, a recent study found that infants are three times more likely to die from Sudden Infant Death Syndrome (SIDS) if their mothers smoke during and after pregnancy, and twice as likely to die if their mothers stop smoking during pregnancy but then resume after birth.

Question 10. EPA Administrator Carol Browner has testified that there are only two ways to effectively protect nonsmokers from involuntary exposure to environmental tobacco smoke: prohibiting smoking indoors, and (2) restricting smoking to rooms that are separately ventilated. Do you agree with Administrator Browner that these two options are the only ones that effectively protect nonsmokers from involuntary exposure to ETS? If so, why aren't other options, such as physically separating smokers from nonsmokers and providing adequate ventilation, sufficiently protective?

Answer. The Department of Health and Human Services (HHS) supports totally smokefree workplaces, and in 1987 instituted a no smoking policy in all space occupied by HHS nationwide. Our smokefree policy is based on evidence of the health effects of exposure to ETS. This includes the conclusion of the 1986 Surgeon General's Report, *The Health Consequences of Involuntary Smoking*, that the simple separation of smokers and nonsmokers within the same air space may reduce, but does not eliminate, the exposure of nonsmokers to environmental tobacco smoke. There is evidence to suggest, that even with separate ventilation, ETS from smoking lounges can still enter nonsmoking areas and that in practice, separate ventilation of designated smoking areas may expose nonsmokers to unacceptable levels of lung cancer risk.

*Question 11.*Has the U.S. Surgeon General's office ever reviewed or commented on the cigarette equivalent approach that the tobacco industry and Congressional Research Service have used to estimate the amount of environmental tobacco smoke to which nonsmokers are exposed? If so, what were its conclusions about the method's ability to accurately assess the amount of ETS exposure to which nonsmokers are exposed?

Answer. The Congressional Research Service (CRS) report uses cigarette equivalents to determine the risk of lung cancer from passive smoking. Cigarette equivalents is not a reliable expression of an assessment of this risk because the complex chemistry of tobacco smoke yields different numbers of cigarette equivalents depending upon the compound being measured. For this reason, scientists at the Department of Health and Human Services and the Environmental Protection Agency consider cigarette equivalents to be an inaccurate and misleading term.

In its assessment of the risk of lung cancer from exposure to ETS, the CRS determines cigarette equivalents by extrapolating from urinary cotinine levels in active compared to passive smokers. Cotinine is the major metabolite of nicotine, measurable in saliva, blood, or urine. It is a primary biological marker for exposure to both mainstream and sidestream (ETS) smoke. Likewise, measuring nicotine from ambient air also is a reliable indoor air quality estimate for the presence of tobacco smoke. But neither measure the risk of lung cancer from exposure to ETS.

When the CRS report used the cigarette equivalent method, it measured nicotine only, and disregarded the other approximately 4,000 constituents of sidestream smoke, many of which are carcinogens. The report concludes that the average exposure of a nonsmoker to ETS is equivalent to smoking 0.1 cigarettes per day, but that measurement is specific to nicotine only. Using this same measurement approach, a nonsmoker exposed to cigarette smoke is getting as much benzene (a known human carcinogen) as a smoker gets in smoking 6 cigarettes, as much 4-aminobiphenyl (another known human carcinogen) as if smoking 17 cigarettes; and as much N-nitrosodimethylamine (a potent animal carcinogen suspected of causing cancer in humans) as if smoking 75 cigarettes. When one looks at the compounds and byproducts found in ETS (many of which are known carcinogens) the cigarette equivalent measures are substantially higher. It is exposure to these' components, and not to nicotine, that is likely to determine the lung cancer risk among exposed nonsmokers.

QUESTIONS BY SENATOR FAIRCLOTH

Question 1. Dr. Blot, you co-authored a 1990 article entitled "Lung Cancer Among Women in Northeast China" that represents one of the largest studies to date on ETS exposure and nonsmoker lung cancer. The data from your study indicate no association between ETS exposures and lung cancer in nonsmoking women in China, yet the EPA's Risk Assessment on ETS criticized this study. Can you address this criticism?

Answer. The study to which you refer, which was conducted in the industrial cities of Shenyang and Harbin in northeast China, was initiated to evaluate the role of intense air pollution (from industrial emissions as well as indoor coal-burning heating sources) in lung cancer development. Levels of benzoapyrene, a carcinogen found in fossil fuel-burning emissions, as well as in cigarette smoke, in some homes in these areas exceeded U.S. outdoor urban standards by 60-fold. Hence, although information on ETS exposures was obtained, the study was not designed to provide a thorough evaluation of the ETS-lung cancer association.

Question 2. Are you aware of any other studies from China on the association of ETS exposure and lung cancer? Explain.

Answer. I am aware of several other studies from China that have reported on the association between ETS exposure and lung cancer. One study by Gao *et al.*[1], of which I also was a co-author, found that the risk of lung cancer among nonsmoking women in Shanghai rose as the years lived with a spouse who smoked increased. A small study by Liu *et al.*[2] found no increased risk associated with ETS in an area of South China with extraordinarily high levels of indoor air pollution from coal-burning stoves in chimney-less houses. A third study by Geng *et al.*[3] reported a doubling of risk of lung cancer among passive smokers. A fourth investigation in Guangzhou by Liu *et al.*[4] also reported a greater than two-fold increase in lung cancer among nonsmoking women whose husbands smoked 20 or more cigarettes per day.

Statistical Significance

Question 3. The EPA's Risk Assessment on ETS looked at a total of 30 studies on spousal smoking and lung cancer from around the world. Didn't 24 of the 30 studies reviewed in the Risk Assessment report overall associations that do not achieve statistical significance, that is, the studies are consistent with no association between spousal smoking and lung cancer risk among nonsmokers?

Answer. Most of the 30 studies reviewed by EPA found overall increases in risk of lung cancer among nonsmoking women married to smokers, but the increases were statistically significant only in a minority of the investigations. In the majority of those studies where information on level of ETS exposure was provided, however, there was a statistically significant trend of rising lung cancer risk with increasing exposure.

Question 4. Eighty percent of the studies on spousal smoking from around the world and all of the American studies published to date report no significant increase in risk for spousal smoking and nonsmoker lung cancer. Given that, why did the EPA feel compelled to go back and "re-analyze" the data in those studies? Is such an endeavor ever driven by science?

Answer. The methodology used by EPA of ascertaining data from multiple studies and combining them in a standardized fashion is appropriate. If this question concerns EPA's policy decisions, it would be best answered by the EPA.

Question 5. The EPA's Risk Assessment on ETS looked at a total of 11 U.S. studies. Isn't it true that *not one* of those studies originally reported an overall statistically significant risk for spousal smoking?

Answer. Although 8 of the 11 U.S. studies showed an overall increase in lung cancer among nonsmoking women married to smokers, the overall excesses were not statistically significant.

Question 6. Not one of the 11 U.S. studies that the EPA considered reported an overall risk that was significantly increased for nonsmoker exposure to ETS. Yet the EPA combined the results from all of those studies and generated an overall risk that was, suddenly, statistically significant. Do you care to explain?

Answer. It is a common epidemiologic practice to combine similar data from multiple studies to provide a summary relative risk estimate. This methodology is known as meta-analysis. The resulting estimate is based on the aggregate data from all the studies. The statistical precision of this average is thus greater than the statistical precision of the individual studies. Hence, the average relative risk may be statistically significant from meta-analysis even though the individual studies are not.

Question 7. Why did the EPA change its test for statistical significance between the list and second draft Risk Assessment? Isn't it true that you only get statistical significance by using the EPA's 90 percent confidence interval and that you do not achieve statistical significance by using the accepted 95 percent confidence interval?

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[1] Gao Y.; Blot, W.J.; Zheng W.; Ershow, A.G.; Hsu C.W.; Levin, L.I. Zhang R.; Fraumeni, J.F. (1987). Lung Cancer among Chinese Women. Int. J. Epidemiol. 40: 604–609.

[2] Liu Z.; Je X.; Chapman, R.S. (1991). Smoking and Other Risk Factors for Lung Cancer in Xuanwei, China. Int. J. Epidemiol. 20: 2631.

[3] Geng G.; Liang Z.H.; Zhang G.L. (1988). On the Relationship Between Smoking and Female Lung Cancer. In: Smoking and Health. Elsevier Science Publishers, pp. 483–486.

[4] Liu Q.; Sasco, M.; Riboli, B.; Xu M.X. (1993). Indoor Air Pollution and Lung Cancer in Guangzhou, People's Republic of China. Am. J. Epidemiol. 137: 145–154.

Answer. The EPA applied one-tailed statistical tests in assessing the significance of the increased relative risk of lung cancer among nonsmokers married to smokers. It is not unprecedented when using one-tailed tests to use 90 percent confidence limits. For example, in studies of the relationship between risk of cancer and exposure to ionizing radiation, a 90 percent confidence interval is standard practice. Although it can be argued whether a one- or two-tailed test (or 90 percent or 95 percent confidence interval) is the most appropriate, the judgement as to whether ETS is a Class A carcinogen was based on many factors (such as consistency, dose response trends, and biological plausibility) and not solely on the type of statistical testing procedure used.

Question 8. Why was the incomplete Fontham study involved? On what basis can this be justified?

Answer. The Fontham study was published in 1991 in the scientific journal, Cancer Epidemiology, Biomarkers, and Prevention. Articles published in this journal are peer-reviewed; the data clearly relevant and thus appropriately included in the EPA review.

Preconceived Notions

Question 9. At one point in the EPA's Risk Assessment, it is stated that lowering the statistical threshold in all the spousal smoking studies is acceptable because "a positive association exists between exposure to ETS and lung cancer". (5–2) Isn't that what the studies are supposed to determine?

Answer. In its evaluation of the relationship between ETS and lung cancer, EPA considered the possibility that ETS may be positively associated with lung cancer (i.e., may increase risk), but not the possibility that ETS may be negatively associated (i.e., may be protective). This seems appropriate since there were no a priori hypotheses that exposure to cigarette smoke' may "reduce the risk of lung cancer.

Question 10. Isn't the Risk Assessment itself supposed to determine whether or not a risk exists, rather than *assume* that it does?

Answer. The risk assessment followed the assumption that if the risk of lung cancer among nonsmokers exposed to ETS were different than the risk of lung cancer among nonsmokers not exposed to ETS, the risk would be higher (not lower) in the ETS-exposed nonsmokers. This is common practice in assessing a potential risk factor for cancer or other diseases.

"Strength" of An Association

Question 11. Why do epidemiologists talk about the "strength" of an association?

Answer. Strength of association is one measure used in assessing the relationship between an exposure and a disease, and evaluating whether the association may be causal. Greater "strength" of an association means that the exposure is more likely to cause the disease.

Question 12. How do you explain an estimated risk of 1.19 in the context of a discussion on "strength" of an association? (The estimated risk of 1.19 is the risk calculated by the EPA for nonsmoker exposure to ETS.)

Answer. From the meta-analysis, the summary relative risk estimate of 1. 19 indicates that nonsmoking women married to smokers may face a 19 percent increase in their risk of developing lung cancer, compared with nonsmokers married to nonsmokers. Epidemiologists would generally consider a relative increase of this magnitude as small, though recognizing that the public health impact of small increases in relative risk can sometimes be large.

Question 13. Don't you agree that, in examining weak associations, issues of bias and confounding are of particular importance?

Answer. Issues of bias and confounding tend to assume greater importance the smaller the actual disease risk from an exposure.

Question 14. Isn't epidemiology suited to detecting strong associations rather than weak associations?

Answer. Epidemiologic studies can more readily detect-stronger associations than weaker associations.

Confounding

Question 15. Researchers from your organization, the National Cancer Institute, recently published one of the largest studies on lung cancer risk in nonsmokers. The authors found that eating foods heavy in saturated fat was strongly associated with increased lung cancer risks, and they said in their paper that "passive smoking did not affect risk estimates in this study." Apparently, this is the first study of its kind to make an adjustment for dietary fat intake. None of the studies that the EPA looked at adjusted for dietary fat. Don't you think this is an important variable that should be considered in any report concerning spousal smoking and lung cancer in nonsmokers?

Answer. The relationship between dietary intake of fat and lung cancer is not clear. The study by Alavanja *et al.*,[5] reported a nearly 6-fold increase in risk associated with high saturated fat consumption, much higher than other studies, but the totality of data to evaluate this issue is limited. Furthermore, the extent of the correlation between fat intake and passive smoking is not well known. Hence, it is not evident that fat intake is an important variable to adjust for in all studies assessing the relation between BTS and lung cancer.

Question 16. What is the range of magnitudes of the relative risks reported in studies of diet and lung cancer?

Answer. The range depends upon which dietary variables are examined. Perhaps the most widely studied dietary item is fruit and vegetable intake, particularly fruits and vegetables high in beta-carotene and other carotenoids. In most studies, the relative risk of lung cancer. among those in the lowest compared to highest quartiles of carotene intake is about 1.5–2.0.

Question 17. Didn't Alavanja and colleagues recently report a relative risk for lung cancer associated with high saturated fat consumption of approximately 6.0?

Answer. Please refer to the answer to Question IS.

Question 18. Shouldn't Alavanja and colleagues present their data according to spousal smokiig status—since their paper and the Brownson study on spousal smoking use the same cases and controls?

Answer. This question could best be addressed by the authors of this study, but it should be possible to conduct analyses of the interrelationships of fat intake, spousal smoking and lung cancer risk.

Omission of Data

Question 19. One of the largest studies on spousal smoking and lung cancer in nonsmokers was published in 1992 and co-authored by researchers from your organization, the National Cancer Institute. This study reported no overall risk increase for nonsmokers exposed to ETS in the home or at work. It was published prior to the release of the EPA's Risk Assessment, yet it was not included within the EPA's calculations in the Risk Assessment. Isn't it true that, had the EPA considered the data in that study, they could not have concluded that spousal smoking leads to a statistically increased risk of lung cancer among nonsmokers?

Answer. The EPA included an Addendum in its report and briefly mentioned the 1992 Brownson *et al.*, study[6] (which Dr. Alavanja of NCI co-authored) as well as the 1992 Stockwell *et al.*, study.[7] The EPA considered these two studies generally consistent with the EPA conclusions. The overall relative risk of lung cancer among nonsmoking women married to smokers was about 1.0 in the Brownson study and 1.6 in the Stockwell study. A crude weighted average (the Brownson study had about twice as many never smokers) of the two would be about 1.2, close to the summary estimate in the EPA report. In addition, each of the Brownson and Stockwell studies found statistically significant increases in risk of lung cancer among nonsmoking women with the highest levels of exposure to ETS. Furthermore, the authors of these studies considered their data to be consistent with the EPA findings. Indeed, the authors of the Brownson study stated in the published abstract, "Ours and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking".

Question 20. Although the EPA claims that the study was published after the "cutoff" date for inclusion, if EPA or other government agencies were looking further at the issue of ETS, wouldn't you agree that any new studies, or studies published after EPA's report was finalized, should be included in their review?

Answer. I would agree that all relevant published studies should be considered in future reviews of ETS.

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[5] Alavanja, M.C.; Brown, C.C.; Swanson, C.; Brownson, R.C. (1993). Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. J. Nad. Cancer Inst. 85: 19061916.

[6] Brownson, R.C.; Alavanja, M.C.; Hock, E.T.; Loy T.S. (1992). Passive Smoking and Lung Cancer in Nonsmoking Women. Am. J. Public Health 82: 1525–1530.

[7] Stockwell, H.G.; Goldman, A.L.; Lyman, G.H.; Noss, C.I.; Armstrong, A.W.; Pinkham, P.A.; Candelora, B.C.; Brusa, M.R. (1992). Environmental Tobacco Smoke and Lung Cancer Risk in Nonsmoking Women. Journal of the National Cancer Institute 84:1417–1422.

Question 21. In your testimony you advised the committee that the Brownson and Stockwell studies were not available in time to include the data in the risk assessment analysis. However, if you were advising the EPA on a risk assessment that it were doing currently, or if OSHA or some other federal agency were doing a risk assessment on ETS, wouldn't you advise that the data from the Brownson and Stockwell studies be included in any meta-analysis or review of the data? Administrator Browner had testified that the EPA had evaluated whether the Brownson data should be included and that the EPA had concluded that inclusion of the Brownson data would not alter the EPA conclusions. As a member of the then-sitting Science Advisory Board, would you have been interested in seeing EPA's documentation of this decision, or would you have been interested in seeing such documentation at present?

Answer. I would recommend that the Brownson and Stockwell studies be included in new meta-analyses or reviews. As indicated in my respond to Question 19, the EPA did provide a brief written comment on the Brownson and Stockwell data in the Addendum to its report.

Workplace Data and Data on Male-Nonsmokers Married to Smokers

Question 22. Nine of the 30 spousal smoking studies looked at by the EPA in their Risk Assessment also analyzed data on male lung cancer risk and spousal smoking, and only one reported an overall statistically significant result. Fourteen of those studies also examined reported workplace exposures to ETS and lung cancer risk, and 12 supported no significant associations. Thirteen of those studies examined childhood ETS exposures and adult lung cancer risk and 12 of the 13 failed to report statistically significant associations. The EPA Risk Assessment failed to look at these data. Aren't those data important, especially when the EPA applied its risk for nonsmoking females in the home to males and to all venues outside the home?

Answer. A number of the studies reviewed by EPA included information on male nonsmokers married to smokers, workplace ETS exposures, and/or childhood ETS exposures. The numbers of lung cancer patients with such data, however, were much less than the numbers of lung cancers among nonsmoking women married to smokers (e.g., less than 100 nonsmoking males cases vs. over 3,000 nonsmoking female cases). Furthermore, there was often less detailed information on workplace or childhood exposure. Although these data are relevant and of interest, the EPA appropriately chose the larger, more informative base of data on nonsmoking women married to smokers upon which to conduct its risk assessment.

Question 23. Isn't it true that the EPA's risk assessment on ETS did not address workplace exposure? Did they not do a meta-analysis of workplace studies?

Answer. The EPA report mentioned but did not consider workplace ETS exposures in its meta-analysis.

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Laboratory of Experimental Atherosclerosis
Arthur Penn, Ph.D., Director

May 25, 1994

Senator Joseph Lieberman
Hart Senate Office Building
Room 502
Washington, DC 20510

Dear Senator Lieberman:

I understand that Senate rules permit information relevant to committee testimony to be included in the public record, if that information is submitted within three weeks of the testimony. If this is correct, I respectfully request that you include the following in the published record.

At the Clean Air and Nuclear Regulation subcommittee meeting on environmental tobacco smoke (ETS) which you chaired on May 11, you received testimony from Dr. Chris Coggins, a toxicologist at R.J. Reynolds. Among the claims he made was one that an individual exposed regularly to ETS for a full year would be exposed to the equivalent mainstream smoke from only 3 cigarettes.

It is important to recognize that while Dr. Coggins often makes this claim and supports it with published findings, both the claim and the stated support for it must be examined critically. For data of this nature to be considered properly, the procedures employed in the ETS measurements must be described clearly (e.g., how many smokers were present, over what period of time smoking was registered, which ETS component was being measured, where the measuring instrument was positioned in relation to the smokers, what were the room dimensions, etc.). Dr. Coggins omits most of these critical facts from his presentations, although he does indicate that the instrumentation used is "very sensitive" or "state of the art".

We have pointed out both publically, including at a recent meeting at which Dr. Coggins was present, and in print that there is a wide range of human exposures to ETS that have been reported in the research literature. The lowest reported levels of exposure (and therefore the ones to which tobacco industry representatives lend a lot of credence) have generally been reported in scientific meeting reports that are not peer-reviewed. Higher levels of exposure to ETS tend to be reported in peer-reviewed scientific journals.

To support his arguments Dr. Coggins often cites a 1993 report in the journal Environment International. While he claims that the results show that there are no differences in the levels of ETS components between smoking and non-smoking venues, the range of values for ETS components presented in this paper tell a different story. It is clear that high levels of ETS have been recorded by investigators in indoor environments (e.g., restaurants).

In addition, the interpretations Dr. Coggins attaches to his own ETS studies with experimental animals at best are naive and at worst are knowingly intended to deceive. As part of the new "ETS is harmless" advertizing campaign launched this week by RJ Reynolds, Coggins claims that rats exposed to levels of ETS 100 times higher than the levels people are exposed to, suffered no deleterious health effects. When Dr. Coggins made this claim recently at the Society of Toxicology meeting in Dallas, we pointed out to both Dr. Coggins and the audience that as far as heart disease is concerned, rats are well known to be a bad model. They just do not get arteriosclerosis. We also pointed out that with all of RJ Reynolds' resources it should have been no trouble for them to test the effects of ETS on animals known to get heart disease, if they really cared about this question. Finally, we disagreed strongly (see the second paragraph below) with Coggins' estimates of human exposure to ETS.

Our own research at NYU has focused on the effects of ETS on the development of arteriosclerosis. Last fall we published a report (see attached document #1) that exposure to ETS alone, without a high fat diet or other stressful factors, resulted in a significant increase in arteriosclerosis in cockerels, an established animal model of the disease. These ETS studies were carried out in specially designed exposure chambers at our Institute. In a second set of experiments in which the ETS dose was reduced to 1/5 the original level, there was still a significantly greater development of arteriosclerosis, compared to the control group.

To compare the animal ETS exposure levels to those that can be encountered routinely in human environments, carbon monoxide (CO), a surrogate for ETS exposure,was measured in the animal exposure chambers and in four smoky bars. We found that when two or more people were smoking simultaneously the CO levels in the bars equalled or exceeded the CO levels we measured in the smoking chambers. Levels of CO, up to five times higher than those found in our animal studies, were recorded in the bars. These findings were presented recently at two meetings (see enclosure #2) and will appear as a full publication in the journal CIRCULATION, later this summer.

The potential human health problems due to ETS exposure extend well beyond the problem of people exposed to ETS in bars. There is considerable evidence (beginning with a landmark study made on autopsied U.S. soldiers killed during the Korean War) that although heart disease is usually associated with middle-aged to aging populations, the disease begins very early in life and its presence can be readily detected in people in their teens or early twenties.

Evidence from our laboratory clearly demonstrates that exposure to ETS accelerates the development of arteriosclerosis. In most indoor venues, especially homes, there is only about one complete air exchange per hour. Thus, indoor air pollutants are not removed rapidly from local environments. Since a) arteriosclerosis begins at a young age b) children have no control over the air they breathe and c) ETS accelerates arteriosclerosis in young animals, our results suggest that children may be at special risk for promotion of the early stages of heart disease by ETS.

Please let me know if there is any further relevant information that I can provide to you.

Sincerely,

Arthur Penn, Ph.D
Research Professor of
Environmental Medicine

[Note: Attachments to this letter have been retained in committee files.]

POW'R Coalition
PUTNAM ** ORANGE ** WESTCHESTER ** ROCKLAND

A TOBACCO CONTROL INITIATIVE

May 15, 1994

Senator Max Baucus, Chairman
511 Hart Senate Office Building
Washington DC 20510

Dear Senator Baucus:

Enviromental tobacco smoke hurts everyone! In terms of human cost, 53,000 innocent victims die each year as a result of their exposure to ETS. This is greater than the total number of deaths from air pollution, water pollution, food additives and radiation combined; more than all automobile accidents, guns, AIDS, and illicit drugs. It's the third major killer in our country.

In economic terms our country would save between 39 to 72 billion dollars in annual expenditures (or about $400 in savings for every U.S. household). The savings would result from lower health costs, fewer premature deaths, and a reduction in employee absenteeism.

The POW'R coalition, a multi-county coalition representing Putnam, Orange, Westchester and Rockland Counties in New York State was formed to reduce tobacco use in our communities. POW'R is part of a national tobacco control initiative. Our mission is to mobilize private, public and community groups to advocate for policy change. Our coalition urges you to support and co-sponsor the Smoke Free Enviroment Act, S.1680, introduced by Senator Lautenberg.

"Cigarettes don't just kill people who smoke. They also kill people who choose not to smoke," said EPA administrator Carol M. Browner.

Here are the facts:

- ETS (Enviromental Tobacco Smoke) has been classified as a Class A carcinogen like asbestos and benzene. This classification means it does cause cancer in humans.
- There is no safe lower limit. ETS causes cancer in non smokers and makes millions sick, causing 37,000 deaths from lung cancer, and 12,000 other cancers.
- ETS presents even greater dangers to our children. Each year it causes:

150,000-300,00 lower respiratory infections
  (pneumonia and bronchitis)
7,500-15,000 hospitalizations
200,000-1,000,000 asthma attacks
8,000-26,000 new asthma cases
A large increase in risk of SIDS (Sudden Infant
  Death Syndrome)

It is crucial you co-sponsor and support S.1680 to protect the public from health hazards caused by exposure to this toxic substance (ETS). Yes, we beleve smokers have rights. No one is advocating that they be banned from having a cigarette in their home, outdoors or car. But, if they are in an enclosed space, with others nearby, their right to smoke comes up against the right of others not to breathe in smoke that may give them disease. This is a public health issue. Please support this bill.

Sincerely,

Denise Higgins

Denise Higgins, Chairperson
Rockland POW'R Coalition

STATEMENT OF ROBERT D. TOLLISON, DUNCAN BLACK PROFESSOR OF ECONOMICS, GEORGE MASON UNIVERSITY

Mr. Chairman and distinguished members of the Committee, my name is Robert B. Tollison. I am Duncan Black Professor of Economics at George Mason University. I have published many articles and books in the field of economics, including *The Economics of Smoking* (1992) and *Clearing the Air: Perspectives on Environmental Tobacco Smoke* (1988). I have served as a Senior Staff Economist at the Council of Economic Advisors and as Director of the Bureau of Economics at the Federal Trade Commission. Although I am appearing at the request of The Tobacco Institute, the views I am expressing are my own.

The focus of my comments is the Environmental Protection Agency's cost-benefit analysis of legislation that would ban or severely restrict smoking in virtually all nonresidential buildings in this country.[1] EPA's cost-benefit results have been widely trumpeted in the press, often with statements that suggest that the underlying analysis is rooted in scientific findings and involves sophisticated econometric modeling. EPA's analysis also is being cited to support legislation (H.R. 3434 and S. 1680) that would ban or severely restrict smoking in virtually all nonresidential buildings in this country.

In fact, EPA's cost-benefit analysis involves the kind of numbers game for which government agencies have been frequently (and I believe justly) criticized. As portrayed in the EPA analysis, the costs of the desired smoking restrictions are *de minimis* while the benefits soar into the billions of dollars. Meanwhile, the agency asserts that the savings it has identified represent a "conservative" estimate, with the reader thus being invited to conclude that the agency has bent over backward to be fair to smokers.

Before describing the bases of my disagreements with EPA, which are many and profound, let me emphasize one area of agreement. EPA correctly observes that cost-benefit analyses can be "useful tools" in helping to identify those government actions that leave society better off while acknowledging that such analyses cannot provide "definitive answers" concerning the merits of such actions (EPA Report, p. ES-1). One central limitation of cost-benefit analyses, of course, is that some "costs" and "benefits" cannot be quantified. To the extent that they are excluded, however, the analyses can be radically incomplete.

For example, EPA's analysis of smoking restriction legislation does not mention, much less attempt to quantify, the damage to liberty that an exercise in social engineering such as that contemplated by H.R. 3434 and S. 1680 would entail. Smoking is not marginal or deviant behavior. Fifty million American adults smoke—about one-quarter of the adult population. Yet, as noted, H.R. 3434 and S. 1680 would eliminate smoking in virtually all public settings—in factories, office buildings and other workplaces; in restaurants, nightclubs, taverns, malls, bingo halls, bowling alleys and pool rooms; in union halls, American Legion facilities and private clubs; in bus stations, train stations and airports; and in hotels and motels.

In short, H.R. 3434 and S. 1680 would substitute a system of official coercion for a system based on, and respectful of, free choice and individually negotiated accommodation. The cost of this abridgment of personal freedom may not be quantifiable. But it is significant, and EPA's willingness to discount it entirely is disturbing.

1. *The History of EPA's Handling of Smoking Issues Raises a Host of Troubling Questions*

Leaving aside the truly unquantifiable, EPA's report on the costs and benefits likely to flow from the imposition of bans or severe restrictions on smoking in most nonresidential buildings raises many troubling questions. Although littered with technical jargon and dealing superficially with a wide range of issues, almost all of the savings projected in EPA's cost-benefit report are in two areas—savings associated with anticipated reductions in the incidence of illness among nonsmokers (between $35 and $66 billion annually) and savings anticipated from reductions in office cleaning and other employee maintenance expenses (between $4 and $8 billion annually).

Adding the "savings" just described, and making only minor adjustments for a few other easily quantifiable consequences of smoking restriction legislation, the EPA report predicts that between $39 and $72 billion will be saved each year in this country if smoking is banned or severely restricted in most indoor environments used by the public. The health-related savings projected by EPA focus on heart disease and lung cancer, with the claimed reduction in the incidence of heart disease among nonsmokers being responsible for most of the health-related "savings" described in the EPA report.

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[1] Indoor Air Division, Office of Radiation and Indoor Air, U.S. Environmental Protection Agency, "The Costs and Benefits of Smoking Restrictions: An Assessment of the Smoke-Free Environment Act of 1993 (H.R. 3434)," April 1994.

Before completing its cost-benefit analysis, EPA had gone on record as an enthusiastic supporter of national smoking restriction legislation. EPA released a "Fact Sheet" calling for smoking bans and/or severe restrictions as early as 1989—4 years before completing its controversial 1993 risk assessment on environmental tobacco smoke ("ETS")[2] In June 1990, three and a half years before EPA had officially declared ETS to be a health hazard, EPA released the first draft of *Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies*, a document encouraging employers to ban smoking in all workplace settings.

With its new cost-benefit analysis, EPA appears finally to have completed the steps one would expect an agency to take when deciding whether to regulate, or seek authority to regulate, a substance or activity. The fact that EPA's regulatory journey occurred in reverse raises, at the very least, questions concerning the objectivity of EPA's belated risk assessment and cost-benefit analysis. The fact that the cost-benefit analysis was prepared by EPA's Indoor Air Division—the same entity that was responsible for EPA's 1989 "Fact Sheet," the draft ETS policy guide and the subsequent risk assessment—only increases the concerns that have been raised concerning EPA's pronouncements concerning ETS.

Questions concerning EPA's ability and/or willingness to address scientific issues in an objective manner are hardly novel. Neither have such questions been limited to EPA's handling of ETS. Concerns about EPA's approach to scientific issues prompted former EPA Administrator William Reilly to convene an expert panel in 1991 to recommend how EPA might improve its performance and reputation. The panel's report, issued in March 1992, noted that "[c]urrently, EPA science is of uneven quality, and the Agency's policies and regulations are frequently perceived as lacking a strong scientific foundation" (*Safeguarding the Future: Credible Science Credible Decisions*, p. 4).

Among the most important of the recommendations made in the *Credible Science Credible Decisions* report was that EPA should seek to avoid "adjusting]" science "to fit policy, either consciously or unconsciously" (p. 38). In initiating a campaign for smoking restrictions before having undertaken, much less completed, either an ETS risk assessment or cost-benefit analysis, EPA ignored the admonitions of the agency's own expert panel—thus opening EPA to the charge of having adjusted science to support a predetermined policy objective.

Former EPA Administrator William Reilly admitted as much when he stated, in response to a congressional inquiry that "beginning the development of an Agency risk assessment after the commencement of work on the draft [ETS] policy guide gave the appearance of the very situation—i.e., policy leading science—that I am committed to avoid" (quoted in Sullum, J., "Just How Bad Is secondhand Smoke?," *National Review* (May 16, 1994), p. 53). Former Administrator Reilly made no effort to defend, either at that time or any other, EPA's distribution beginning in 1989 of the EPA "Fact Sheet" on ETS, which contains assertions and policy recommendations even more extreme than those contained in the final risk assessment and policy guide.

The evidence of bias, of fitting science to a preordained policy, serious in any circumstances, takes on added force in view of the report issued in March 1994 by the Congressional Research Service ("CRS") entitled *Cigarette Excise Taxes to Fund Health Care Reform: An Economic Analysis*. The CRS report concludes that increasing the cigarette excise tax based on claims by EPA and others that smoking impairs the health of nonsmokers cannot be justified. According to the CRS report, if ETS has any effects at all—particularly in a nonresidential context, which is the focus of EPA's cost-benefit analysis—the effects "would be quite small" (CRS Report, p. 13).

The CRS report also summarizes some of the issues that must be resolved before ETS can be said to pose a risk to nonsmokers and notes, quite correctly, that the studies upon which EPA relied in preparing its ETS risk assessment are studies "within the home, not in the workplace or in public places" (CRS Report, p. 10 n. 14). Yet it is the workplace and public places that are the focus of the EPA cost-benefit analysis, environments that are ignored in the ETS risk assessment document that EPA released in January 1993.

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[2] Indoor Air Division, Office of Radiation and Indoor Air, U.S. Environmental Protect ion Agency, "Indoor Air Facts Number 5" (1989); Indoor Air Division, Office of Radiation and Indoor Air, U.S. Environmental Protection Agency, Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders," January 7, 1993.

Finally, the CRS took EPA to task for having lowered conventional standards in assessing ETS, noting that "it is unusual to return to a study after the fact, lower the required significance level, and declare its results to be supportive rather than unsupportive of the effect one's theory suggests should be present" (CRS Report, p. 47). The only justification that EPA has offered for utilizing a relaxed standard in assessing the possible health implications of ETS is "the a *priori* hypothesis . . . . that a positive association exists between exposure to ETS and lung cancer" (EPA Risk Assessment, p. 5–2). Obviously, that purported justification is precisely the "verdict first, trial later" approach that the *Credible Science* report lamented and recommended that EPA seek to avoid.

2. *EPA's Treatment of Heart Disease Is Specially Revealing*

For reasons never adequately explained, EPA assumes in its cost-benefit analysis that eliminating exposure to ETS in workplaces and in public places would reduce significantly the incidence of heart disease among nonsmokers. In fact, between 80 and 90 percent of the mortality cost savings included in EPA's figures are directly attributable to purportedly avoided heart disease deaths. (EPA Report, pp. 12–13 and Exhibits 2–4.) Savings attributable to EPA's hypothesized decrease in the incidence of heart disease among nonsmokers account for the overwhelming majority of *all* dollar benefits estimated by EPA to be associated with national smoking restriction legislation.

Although EPA's claims concerning heart disease "savings" are objectionable on a number of grounds, the decisive objection is that neither EPA nor any other federal agency has concluded that ETS is a *cause* of heart disease. EPA does not in its cost-benefit report argue to the contrary. EPA asserts in its report only that the evidence "suggest[s] a possible link" between exposure to ETS and heart disease (EPA Report, p. 11) . "Suggests," of course, is not the same as "demonstrates," "possible" is not the same as "probable," and "link" is not the same as "cause."

Although one might have expected the discussion of heart disease to end at that point, the drafters of the report appear somehow to have forgotten their original concession concerning ETS and heart disease by the time they were ready to begin their calculations. Using mortality figures developed by Wells and Steenland and endorsed by the American Heart Association ("AHA"), EPA proceeds to make a series of arbitrary "adjustments." First, EPA adopts the low end of the AHA range as its high estimate for potentially avoided heart disease deaths. Second, it reduces that figure by 50 percent to obtain a low estimate. Next, EPA makes "an arbitrary additional adjustment of 75 percent," never even attempting to explain the basis of or possible reasons for such an adjustment. Finally, EPA assumes, without the slightest justification, that a very precise sounding 73 percent of ETS-related heart disease deaths are attributable to non-home exposures. (EPA Report, pp. 12–13.)

One does not have to be an economist to see that the exercise just described lacks any semblance of meaning. If the figures endorsed by the AHA are truly believable, despite the absence of prior governmental endorsement, why not use those figures as is? To obtain a low estimate, why not reduce the AHA's figures by 10 percent rather than 50—or by 90 percent? Further, why be content with the assumption that only 73 percent of avoidable heart disease deaths result from non-home exposure to ETS? Why not 80 or 90 percent? One searches EPA's cost-benefit analysis in vain for answers to any of those questions.

After having made the adjustments just described, the drafters of the EPA cost-benefit analysis suggest that such adjustments justify their characterizing the heart disease related "savings" identified in the report as "conservative." True conservatism, of course, should have led them to exclude altogether any claimed savings from avoided heart disease deaths.

3. *EPA's Assertions Concerning Childhood Diseases Also Are Unsupportable*

The claims in EPA's cost-benef it report concerning childhood diseases said to be exacerbated by exposure to ETS also ignore several critical considerations. Even if one assumes for discussion purposes that prolonged childhood exposure to ETS can pose a health risk—a quite controversial assumption—the consequent "savings" identified by EPA appear to be phantom benefits.

As EPA acknowledges (EPA Report, p. 3 n. 1), recently enacted federal legislation bans smoking in all facilities used to provide federally-supported kindergarten, elementary or secondary education or library services to children as well as in the portions of all other facilities used to provide federally-supported health, day care or early childhood development services.[3] Since those are the indoor venues in which children spend most of their time when they are not at home, further smoking restriction legislation such as H.R. 3434 and S. 1680 (which would not prohibit smoking in the home) could not produce the improved health benefits to children claimed in EPA's cost-benefit analysis.

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[3] Goals 2000: Educate America Act, Public Law No. 103–227, § 1043 108 Stat. 125, 272 (1994) (to be codified at 20 U.S.C. § 6083)

EPA justifies including such "savings" on the ground that "a sensitivity analysis is presented of alternative base-line assumptions" (EPA Report, ES-3 n. 1). That is essentially double talk. A "sensitivity analysis" is a hollow gesture when, as here, the facts reduce to an empty promise the entire category of supposed health benefits. The recently-enacted federal legislation concerning smoking and children should have caused EPA to remove this category entirely from its calculations.

4. The "Savings" Claimed for Employee Maintenance Costs Are as Arbitrary as Health Related "Savings" Computed by EPA

The other major area of savings claimed by EPA to be associated with a smoking ban or severe restrictions consists of an estimated $4 to $8 billion in office cleaning and other employee maintenance costs. According to EPA:

"Smoking in a building involves operational and maintenance expenses. In addition to emptying and cleaning ashtrays, the smoke, ashes, and accidental burns on furniture and carpets create an additional housekeeping and general maintenance burden" (EPA Report, p. 32).

A few preliminary observations concerning employee "maintenance" costs may be useful. All employees, whether or not they smoke, impose a variety of maintenance costs on employers—from spilled coffee on the carpet to broken coat hangers in the closet. Employers could reduce such maintenance costs across the board by prohibiting all sorts of behaviors in the workplace, from drinking and eating to wearing shoes inside on rainy or snowy-days. If the goal is to reduce the cost of maintaining employees to zero, employers could require all employees to work at metal desks, seated on metal chairs, and could eliminate other amenities as well.

From a societal standpoint, the maintenance costs associated with most personal behaviors in the workplace are trivial when compared to the intrusiveness of prohibitions against them. A decision to ban smoking to reduce the cost of cleaning draperies is no different in kind from a decision to prohibit the drinking of coffee in the office to reduce damaging or unsightly spills. Each such decision involves a tradeoff between employer cost and employee comfort and satisfaction. If the goal is to reduce employee maintenance costs, employers would be well advised to focus on marginal areas not relating to human activity or personal comfort before regulating employees who happen to drink coffee or soft drinks or who happen to smoke.

What maintenance costs an enlightened employer should tolerate is an issue best left, I would suggest, to the good judgment and common sense of individual employers. As I stated in my 1992 book with Dr. Richard Wagner (*The Economics of Smoking*, p. 64):

"Employers, of course, have incentives to mitigate accidental damage to property, whether by smokers or nonsmokers. But the kinds of accounting statistics commonly reported in these matters give no convincing basis for concluding that smokers are a source of excess property damage. And in any event, the issues created are ones of individual business policy and not of public policy, for it is the owners of the businesses who bear whatever costs may be incurred."

Even if one ignores the philosophical problem just discussed, EPA's assertions concerning the employee maintenance costs assertedly associated with smoking defy common sense. If $8 billion (or even $4 billion) in employee maintenance savings are readily available, why have American managers not captured those savings, transferring them directly to the bottom line? The managers of businesses in this country are not unintelligent, for if they were they would not be in business very long. Is it not conceivable that the owners and managers of the many business establishments in this country have a better handle on employee maintenance costs than do the drafters of the EPA cost-benefit report?

The $4 to $8 billion in employee maintenance cost savings projected by EPA appear to be based in large part upon a report from a single company said to have experienced "a 15 percent reduction in housekeeping costs when a non-smoking policy was introduced" (EPA Report, p. IS). The EPA report contains no data or information that would permit an objective reader to assess the validity or representativeness of that reported reduction. Without such information, the entire discussion in the report of possible employee maintenance savings—even when considered on its own terms and without regard to philosophical considerations—is uninterpretable.

5. *EPA's Estimates of Savings From Reduced Absenteeism and Smoking-Related Fires Also Are Unfounded*

As noted above, the other benefits touted in the EPA report are small and inconsequential relative to the purported health benefits. But EPA's discussion of those other benefits is also rife with error.

Reduced Absenteeism. On the assumption that smokers miss work more frequently than nonsmokers due to their smoking, and that banning smoking would lead some smokers to quit, EPA estimates that those who quit would realize an additional $0.5 billion in earnings due to "reduced absenteeism" (EPA Report, pp. 32–33). But it has not been established that smokers miss work more frequently than nonsmokers due to their smoking. The large majority of studies that report an association between smoking status and increased employee absenteeism acknowledge that factors other than smoking may account for any association. As James Athanasou, an antismoking advocate, has stated:

"Sickness absence is a complex behavioral phenomenon in which a multiplicity of health, social and psychological factors are involved. . . . . Most investigators have implicitly assumed that the only difference between a nonsmoking and a smoking group is their tobacco habit and that any other personal factors are equally distributed within these groups. . . . . None of the reported studies has considered the additional effects on sickness absence of job satisfaction, attitudes to work, personality, other psychosocial or socioeconomic variables and the urban factor in conjunction with the effects of smoking."[4]

In our own book on the subject, Richard E. Wagner and 1 likewise noted that smokers and nonsmokers are not identical in all respects other than smoking. Among other things, smokers have an above-average representation in blue collar occupations, they tend to consume an above-average amount of alcohol, and they generally exercise less than nonsmokers. In assuming that people are identical except for their smoking, various diseases and their associated costs are often improperly attributed to smoking.[5] Professor Richard Ault of Auburn University and several colleagues similarly have noted that the failure to consider the many differences between smokers as a group and nonsmokers as a group has resulted in "spurious conclusions about the relationship between smoking and absenteeism."[6]

Savings in Smoking-Related Fires. Recognizing that "most smoking-related fire injuries and property losses are in residential environments," which would not be affected by legislation such as H.R. 3434 and S. 1680, EPA nevertheless estimates that such legislation would result in savings of $0.5-$0.7 billion per year from avoided smoking-related fires. (EPA Report, p. 19.) That is, in large measure, another phantom savings, for EPA ignores the fact that existing fire codes already prohibit smoking in those venues where smoking is likely to be a fire hazard. In addition, EPA attributes some savings to residential fires that would not occur because smoking ban legislation would lead some smokers to quit altogether. That portion of the estimated savings assumes that those smokers whom the legislation could lead to quit are those most likely to be involved in cigarette-related fires in the home. No support for that assumption can be found in EPA's analysis.

6. *EPA Has Understated Substantially the Costs of Smoking Bans and Severe Restrictions*

Rather than being content with providing an unrealistically low figure for the cost of creating smoking lounges in public places and in the workplace, thereby avoiding a large reduction in purported smoking ban benefits, the drafters of the EPA cost-benefit report seem intent on discouraging any accommodation of smokers. According to the report, "smoking policies involving smoking lounges are generally associated with greater complaints and with lower reported satisfaction than smoking bans, and smoking bans are becoming increasingly popular . . . ." (EPA Report, p. ES-4).

No explanation appears in the EPA report for such a surprising conclusion. If, as EPA has assumed, smoking lounges are required to be constructed so that no smoke can escape to nonsmoking areas (a result that is to be accomplished by maintaining smoking lounges under negative pressure in relation to adjacent areas and exhausting smoke directly to the outside), it is difficult to understand why any nonsmoker would object to the creation of a smoking lounge. Equally to the point, why would smokers object to being provided a smoking lounge when confronted with a rule prohibiting smoking at their workstation?

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[4] Athanasou, James A., "Sickness Absence and Smoking Behavior and Its Consequences," *Journal of Occupational Medicine* (1975), vol. 17, p. 444.

[5] Tollison, Robert D. and Wagner, Richard E., *The Economics of Smoking* (1992), p. 64.

[6] Ault, Richard W., et al., "Smoking and Absenteeism," *Alied Economics* (1991), vol. 23, pp. 743, 751–52

Similarly, the EPA report asserts that any smoking breaks demanded by smokers not permitted to smoke at their workstation are not likely to entail significant costs. According to the EPA report, "[t]he resulting effect on productivity would be limited because taking occasional breaks is already a normal part of the workday for most persons" (EPA Report, p. ES-10). The report then attempts to justify ignoring such costs entirely by noting that they "would be difficult to quantify" (*ibid.*)

A quick drive through the streets of Washington, DC, could readily have confirmed the invalidity of claims that smoking breaks have no measurable or meaningful impact on worker productivity. One can easily identify where smoking has been banned in downtown Washington. The evidence is in the substantial number of people smoking, sometimes for extended periods, near the entrances of major office buildings. That is precisely what would happen, albeit on a much larger scale, if the legislation envisaged by EPA were enacted.

One might reasonably assume, for example, two 15 minute breaks for smoking workers per day (in addition to the break provided by the luncheon period). That amounts to 1/16 of a normal working day. One also might reasonably assume comparable breaks for nonsmoking employees being required on equity grounds. Even without performing any further calculations, it should be apparent that the resulting productivity losses would run into many tens of billions of dollars per year. Indeed, if done carefully, the cost estimate resulting from such an analysis likely would overwhelm EPA's net benefit estimates. Although the assumptions at the base of any such calculation may be somewhat arbitrary, they would be no less realistic than many of the assumptions on which EPA has based its net benefits case.

Furthermore, it is the task of individual business owners to determine how best to operate their businesses. Firms have clear incentives to produce the maximum output at the lowest possible cost. In this respect, even if smokers are more costly to employers than nonsmokers (a point for which I believe no convincing evidence exists), they will be employed because they add more to a firm's revenues than to its costs. To focus on the alleged costs of hiring a particular type of worker is beside the point. An employer's interest always will be best served by hiring the best workers, among whom smokers often will be found. Thus, whether through open competition for workers or through collective bargaining, the proper approach to workplace smoking is to allow companies and employees to find the appropriate smoking policy on a company-by-company basis.

7. *The Private Sector Has Sufficient Incentives To Handle ETS on Its Own*

Consider ETS in the context of privately-owned public places. The bar, the restaurant, the airline and other firms are privately-owned entities. In each case, the owner has an economic interest in providing an environment that workers and customers find desirable. For example, firms hiring employees in a competitive labor market will control the workplace environment as part of an optimizing compensation package. That may involve smoker-nonsmoker segregation on the job, investment in smoke-removal devices, paying smokers or nonsmokers a wage premium to work in a given environment, and so on. The bottom line is that the owner will internalize such costs.

Suppose that all workers prefer to smoke on the job but the owner strongly objects to smoking. Clearly, the owner must bear the costs of indulging his preference. If he prohibits smoking on the job and offers only the going market wage, no smoker is likely to be willing to work for him. To induce his employees not to smoke, the owner must pay a premium that is sufficient to make employment at his firm as attractive as alternative positions without smoking restrictions. On the other hand, the owner can offer the market wage, allow smoking on the job, and invest in smoke-removal devices that improve air quality. In either case, the costs of imposing a given smoking policy are internal to the firm.

Now, suppose that the owner is indifferent insofar as smoking is concerned but that some workers wish to smoke on the job while others prefer workplace smoking restrictions? How does the owner reconcile those conflicting preferences? One option would be to ban smoking on the job and compensate smokers accordingly. Yet other options would be to segregate smoking and nonsmoking employees or to install smoke-removal equipment. Which of those options the employer chooses ultimately will depend on such factors as the mix of smokers and nonsmokers in the firm's workforce, the cost and effectiveness of air cleaners, and the nature of the firm's production process. The last consideration may affect, of course, the extent to which co-workers can be separated without adversely affecting overall productivity. Market forces will lead the owner to select the smoking policy that achieves the desired result at minimum cost. In a competitive market, we would expect, therefore, to observe a variety of smoking policies that take into account the unique circumstances of individual firms and their employees.

Exactly the same argument applies to the owner of a restaurant, bar or any other private firm that serves a public comprised of smokers and nonsmokers. The market for dining out, for example, will discipline firms in the restaurant industry to provide preferred eating and drinking environments. That necessarily involves the mechanisms mentioned previously; smoker-nonsmoker segregation, smoke removal devices, price-environmental trade-offs, and so on. If the owner bans smoking, smokers will only patronize the establishment if the price-quality combination offered is more attractive than the price-quality combination offered in eating places where smoking is allowed. The opposite applies for nonsmokers if smoking is permitted. The owner can indulge his own preferences at a cost. Thus, a variety of smoking policies will arise in the marketplace and, in the process, issues related to smoking in restaurants and bars will be minimized.

In sum, EPA's cost-benefit analysis is fundamentally flawed. The analysis lacks a convincing scientific basis, its estimates of costs and benefits are skewed, and the incentives so obviously at work in the private sector for dealing with smoking in an appropriate manner are unjustifiably ignored.

II

103D CONGRESS
1ST SESSION

S. 262

To require the Administrator of the Environmental Protection Agency to promulgate guidelines for instituting a nonsmoking policy in buildings owned or leased by Federal agencies, and for other purposes.

IN THE SENATE OF THE UNITED STATES

JANUARY 28 (legislative day, JANUARY 5), 1993

Mr. LAUTENBERG (for himself and Mr. HARKIN) introduced the following bill; which was read twice and referred to the Committee on Environment and Public Works

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A BILL

To require the Administrator of the Environmental Protection Agency to promulgate guidelines for instituting a nonsmoking policy in buildings owned or leased by Federal agencies, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Preventing Our Federal Building Workers and Visitors From Exposure to Deadly Smoke (PRO–FEDS) Act of 1993".

SEC. 2. FINDINGS.

Congress finds that—

(1) environmental tobacco smoke comes from secondhand smoke exhaled by smokers and sidestream smoke emitted from the burning of cigarettes, cigars, and pipes;

(2) since citizens of the United States spend up to 90 percent of a day indoors, there is a significant potential for exposure to environmental tobacco smoke from indoor air;

(3) exposure to environmental tobacco smoke occurs in schools, public buildings, and other indoor facilities;

(4) recent scientific studies have concluded that exposure to environmental tobacco smoke is a cause of lung cancer in healthy nonsmokers and is responsible for acute and chronic respiratory problems and other health impacts in sensitive populations (including children);

(5) the health risks posed by environmental tobacco smoke exceed the risks posed by many environmental pollutants regulated by the Environmental Protection Agency; and

(6) according to information released by the Environmental Protection Agency, environmental tobacco smoke results in a loss to the economy of over $3,000,000,000 per year.

SEC. 3. DEFINITIONS.

As used in this Act:

(1) ADMINISTRATOR.—The term "Administrator" means the Administrator of the Environmental Protection Agency.

(2) EXECUTIVE AGENCY.—The term "Executive agency" has the meaning provided in section 105 of title 5, United States Code.

(3) FEDERAL AGENCY.—The term "Federal agency" includes any Executive agency, the Executive Office of the President, any military department, any court of the United States, the Administrative Office of the United States Courts, the Library of Congress, the Botanic Garden, the Government Printing Office, the Congressional Budget Office, the United States Postal Service, the Postal Rate Commission, the Office of the Architect of the Capitol, the Office of Technology Assessment, and any other agency of the executive, legislative, and judicial branches.

(4) FEDERAL BUILDING.—The term "Federal building" means any building or other structure owned or leased for use by a Federal agency, except that the term shall not include any area of a building that is used primarily as living quarters.

(5) SECRETARY.—The term "Secretary" means the Secretary of Health and Human Services.

SEC. 4. NONSMOKING POLICY FOR FEDERAL BUILDINGS.

(a) IN GENERAL.—

(1) ISSUANCE OF GUIDELINES.—Not later than 180 days after the date of enactment of this Act, the Administrator shall issue guidelines for instituting and enforcing a nonsmoking policy at each Federal agency.

(2) CONTENTS OF GUIDELINES.—A nonsmoking policy that meets the requirements of the guidelines shall, at a minimum, prohibit smoking in each indoor portion of a Federal building that is not ventilated separately (as defined by the Administrator) from other portions of the facility.

(b) ADOPTION OF GUIDELINES.—

(1) IN GENERAL.—As soon as is practicable after the date of issuance of the guidelines referred to in subsection (a), the head of each Executive agency, and the Director of the Administrative Office of the United States Courts shall adopt a nonsmoking policy applicable to the Federal agency under the jurisdiction of the individual that meets the requirements of the guidelines referred to in subsection (a), and take such action as is necessary to

ensure that the policy is carried out in the manner specified in the guidelines.

(2) Legislative branch.—As soon as is practicable after the date of issuance of the guidelines referred to in subsection (a), the following entities and individuals shall adopt a nonsmoking policy that meets the requirements of the guidelines referred to in subsection (a), and take such action as is necessary to ensure that the policy is carried out in the manner specified in the guidelines:

(A) With respect to the House of Representatives (including any office space or buildings of the House of Representatives), the House Office Building Commission.

(B) With respect to the Senate (including any office space or buildings of the Senate), the Committee on Rules and Administration of the Senate.

(C) With respect to any other area occupied or used by a Federal agency of the legislative branch, the Architect of the Capitol.

(3) Certification for executive agencies.—The Administrator of General Services, in consultation with the Administrator, shall review each nonsmoking policy adopted by the head of an

Executive agency and shall certify those policies that meet the requirements of the guidelines referred to in subsection (a). In carrying out the certification, the Administrator of General Services shall use a procedure and apply criteria that the Administrator shall establish. Except as provided in subsection (c), if a policy does not meet the requirements of the guidelines, the Administrator of General Services shall—

(A) in a written communication, advise the head of the Executive agency concerning modifications of the policy to meet the requirements; and

(B) publish the communication in the Federal Register.

(c) WAIVERS.—

(1) EXECUTIVE AGENCIES.—The head of an Executive agency may publicly petition the Administrator of General Services for a waiver from instituting or enforcing a nonsmoking policy (or policy requirement) under the guidelines issued pursuant to subsection (a). The Administrator of General Services may waive the requirement if, after consultation with the Administrator, the Administrator of General Services determines that—

(A) unusual extenuating circumstances prevent the head of the Federal agency from enforcing the policy (or a requirement under the policy) (including a case in which the Federal agency shares space in an indoor facility with a non-Federal entity and cannot obtain an agreement with the other entity to abide by the nonsmoking policy requirement) and the head of the Executive agency will establish and make a good-faith effort to enforce an alternative nonsmoking policy (or alternative requirement under the policy) that will protect individuals from exposure to environmental tobacco smoke to the maximum extent possible; or

(B) the head of the Executive agency will enforce an alternative nonsmoking policy (or alternative requirement under the policy) that will protect individuals from exposure to environmental tobacco smoke to the same degree as the requirement under the guidelines issued pursuant to subsection (a).

(2) AGENCIES OF THE JUDICIAL BRANCH.—After consultation with the Administrator, and after providing public notice and reasonable opportunity for public review and comment, the Director of the

Administrative Office of the United States Courts may, on the basis of the criteria for a waiver referred to in paragraph (1), make such modifications to the nonsmoking policy required to be carried out pursuant to subsection (b) as the Director determines to be necessary. The Director may not make any modification that violates the criteria for a waiver under paragraph (1).

(3) AGENCIES OF THE LEGISLATIVE BRANCH.—After consultation with the Administrator, and after providing public notice and reasonable opportunity for public review and comment, the appropriate entity or individual referred to in subparagraphs (A) through (C) of subsection (b)(2) may, on the basis of the criteria for a waiver referred to in paragraph (1), make such modifications to the nonsmoking policy required to be carried out pursuant to subsection (b) as the entity or individual determines to be necessary. The entity or individual may not make any modification that violates the criteria for a waiver under paragraph (1).

(d) COLLECTIVE BARGAINING AGREEMENTS.—

(1) IN GENERAL.—In a Federal agency in which a labor organization has been accorded recognition as a bargaining unit pursuant to chapter 71

of title 5, United States Code, the Federal agency shall engage in collective bargaining pursuant to section 7114 of title 5, United States Code, to ensure the implementation of the requirements of this section that affect work areas predominately occupied by the employees represented by the labor organization by the date of the adoption, pursuant to this section, of a nonsmoking policy applicable to the Federal agency.

(2) EXEMPTION.—

(A) IN GENERAL.—If, on the date of enactment of this Act—

(i) a bargaining unit referred to in paragraph (1) has in effect a collective bargaining agreement with respect to which a Federal agency is a party; and

(ii) the collective bargaining agreement referred to in clause (i) includes provisions relating to smoking privileges that are in violation of the requirements of this section,

the head of the Federal agency may exempt work areas predominately occupied by the employees subject to the collective bargaining agreement from the nonsmoking policy that the

Federal agency is required to be carried out under subsection (b).

(B) TERMINATION OF EXEMPTION.—

(i) IN GENERAL.—An exemption referred to in subparagraph (A) shall terminate on the earlier of—

(I) the first expiration date (after the date of enactment of this Act) of the collective bargaining agreement containing the provisions relating to smoking privileges; or

(II) the date that is 1 year after the date of issuance of the guidelines.

(ii) IMPLEMENTATION OF NONSMOKING POLICY AFTER TERMINATION DATE.— By the applicable date specified in clause (i)(II), the head of each Federal agency shall be required to enforce a nonsmoking policy that meets the requirements of the guidelines issued under subsection (a) in each work area under the jurisdiction of the head of the Federal agency, notwithstanding any collective bargaining agreement that contains provisions that are less restrictive than the nonsmoking policy.

SEC. 5. TECHNICAL ASSISTANCE AND OUTREACH ACTIVITIES.

(a) TECHNICAL ASSISTANCE.—The Administrator and the Secretary shall provide technical assistance to the heads of Federal agencies and other persons who request technical assistance. The technical assistance shall include information—

(1) on smoking cessation programs for employees; and

(2) to assist in compliance with the requirements of this Act.

(b) OUTREACH ACTIVITIES.—

(1) IN GENERAL.—The Administrator, in consultation with the Secretary, shall establish an outreach program to inform the public concerning the dangers of environmental tobacco smoke. As part of the outreach program, the Administrator and the Secretary shall make available to the general public brochures and other educational materials. In establishing the programs under this paragraph, the Administrator and the Secretary shall cooperate to maximize the sharing of information and resources.

(2) ENVIRONMENTAL TOBACCO SMOKE ADVISORY OFFICE.—

(A) IN GENERAL.—The Administrator shall establish within the Office of Radiation and Indoor Air of the Environmental Protection Agency an office, to be known as the "Environmental Tobacco Smoke Advisory Office". The Administrator shall appoint a Director to carry out the functions of the office.

(B) DUTIES OF THE DIRECTOR.—The Director shall—

(i) provide information on smoking cessation;

(ii) provide information to assist in compliance with the requirements of this Act;

(iii) provide information on the dangers of environmental tobacco smoke to any person who requests the information;

(iv) establish a telephone hotline to provide information on the dangers of environmental tobacco smoke; and

(v) carry out any other function of the Office that the Administrator determines to be appropriate.

SEC. 6. REPORT BY THE ADMINISTRATOR.

Not later than 2 years after the date of enactment of this Act, the Administrator shall submit a report to Congress that includes—

(1) information concerning the degree of compliance with this Act; and

(2) an assessment of the legal status of smoking in public places.

SEC. 7. PREEMPTION.

Nothing in this Act is intended to preempt any provision of law of a State or political subdivision of a State that is more restrictive than a provision of this Act.

O

103D CONGRESS
1ST SESSION

S. 1680

To amend the Toxic Substances Control Act to protect the public from health hazards caused by exposure to environmental tobacco smoke, and for other purposes.

IN THE SENATE OF THE UNITED STATES

NOVEMBER 18 (legislative day, NOVEMBER 2), 1993

Mr. LAUTENBERG introduced the following bill; which was read twice and referred to the Committee on Environment and Public Works

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A BILL

To amend the Toxic Substances Control Act to protect the public from health hazards caused by exposure to environmental tobacco smoke, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Smoke-Free Environment Act of 1993".

SEC. 2. UNIFORM INDOOR AIR POLICY.

(a) IN GENERAL.—The Toxic Substances Control Act (15 U.S.C. 2601 et seq.) is amended by adding at the end the following new title:

"TITLE V—UNIFORM INDOOR AIR POLICY WITH RESPECT TO ENVIRONMENTAL TOBACCO SMOKE

"SEC. 501. PURPOSE.

"The purpose of this title is to establish a uniform indoor air standard for public facilities with respect to environmental tobacco smoke.

"SEC. 502. DEFINITIONS.

"As used in this title:

"(1) ENVIRONMENTAL TOBACCO SMOKE.—The term 'environmental tobacco smoke' means smoke emitted from a cigarette, cigar, or pipe, or any other combustion of tobacco.

"(2) PUBLIC FACILITY.—The term 'public facility'—

"(A) means a building regularly entered by 10 or more individuals at least 1 day per week, including a building owned by or leased to a Federal, State, or local government entity; and

"(B) does not include a building or portion of a building regularly used for residential purposes.

"(3) RESPONSIBLE ENTITY.—The term 'responsible entity' means, with respect to a public facility, the owner of the facility, except that in the case of a facility or portion of a facility that is leased, the term means the lessee of the facility.

"SEC. 503. UNIFORM INDOOR AIR POLICY.

"(a) REQUIREMENT OF POLICY.—

"(1) IN GENERAL.—Except as provided in subsection (b), the responsible entity for each public facility shall adopt and carry out at the facility a uniform indoor air policy that meets the requirements of paragraph (2).

"(2) ELEMENTS OF POLICY.—

"(A) IN GENERAL.—Except as provided in subparagraph (B), each uniform indoor air policy for a public facility shall—

"(i) prohibit the emission of environmental tobacco smoke within the facility and on facility property within the immediate vicinity of the entrance to the facility; and

"(ii) post a clear and prominent notice of the prohibition specified in clause (i) in appropriate and visible locations at the public facility.

"(B) EXCEPTION FOR SPECIALLY DESIGNATED SMOKING AREAS.—

"(i) IN GENERAL.—A uniform indoor air policy may provide an exception to the prohibition specified in subparagraph (A)(i) for 1 or more specially designated smoking areas within a public facility if each area meets the requirements of clause (ii).

"(ii) REQUIREMENTS.—An area meets the requirements for a specially designated smoking area referred to in clause (i) if—

"(I) the area is ventilated in accordance with specifications issued by the Administrator that ensure that air from the area is directly exhausted to the outside and does not recirculate or drift to other areas within the public facility; and

"(II) nonsmoking individuals do not have to enter the area for any purpose.

"(b) WAIVERS.—

"(1) IN GENERAL.—A responsible entity for a public facility may petition the Administrator for a waiver from compliance with subsection (a). If the Administrator determines that the public facility is subject to unusual and extenuating circumstances that prevent the compliance, the Administrator may grant the waiver and instead require that the facility protect nonsmokers to the maximum extent practicable.

"(2) TERM OF WAIVER.—Each waiver granted under this subsection shall be for a period of not to exceed 1 year.

"(3) PUBLICATION.—Each petition for a waiver and a summary of subsequent actions taken by the Administrator shall be published in the Federal Register.

"(4) REPORT TO CONGRESS.—The Administrator shall annually report to Congress on all waivers granted during the preceding year.

"SEC. 504. ENFORCEMENT.

"(a) PENALTIES.—

"(1) IN GENERAL.—A person subject to section 503 who fails to comply with such section shall be liable to the United States for a civil penalty in an amount not to exceed $5,000 for each day during which the violation continues.

"(2) USE OF PENALTIES.—A court may order that a civil penalty imposed under this section be used for projects that further the purpose of this title. The court shall obtain the view of the Administrator in determining whether to issue an order described in the preceding sentence and in selecting the projects.

"(b) BRINGING OF ACTIONS.—

"(1) IN GENERAL.—Subject to paragraph (2), an action to enforce section 503 may be brought by a person aggrieved by a violation of such section, a State or local government agency, or the Administrator.

"(2) NOTICE.—An aggrieved person referred to in paragraph (1) shall give an alleged violator notice of the alleged violation not less than 60 days before bringing an action under this section. An aggrieved person may not bring an action under this section if the alleged violator complies with section 503 within the 60-day period and thereafter.

"(c) VENUE.—An action to enjoin a violation of section 503 or to impose a civil penalty for a violation of such section may be brought in a district court of the United States for the district in which the defendant resides or is doing business. The district court shall have jurisdiction, without regard to the amount in controversy or the citizenship of the parties, to enforce section 503 and to impose civil penalties under this section.

"(d) COSTS.—In issuing a final order in an action brought under this section, a court may award costs of litigation (including reasonable attorney and expert witness fees) to a prevailing plaintiff, if the court determines that the award is appropriate.

"SEC. 505. PREEMPTION.

"Nothing in this title shall preempt or otherwise affect any other Federal, State, or local law that provides protection from health hazards from environmental tobacco smoke.

"SEC. 506. REGULATIONS.

"The Administrator may issue such regulations as the Administrator considers necessary to carry out this title.".

(b) EFFECTIVE DATE.—This section and the amendment made by this section shall become effective on the date that is 1 year after the date of enactment of this Act.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 23 1994

OFFICE OF CONGRESSIONAL
AND LEGISLATIVE AFFAIRS

The Honorable Joseph I. Lieberman
Chairman
Subcommittee on Clean Air and Nuclear Regulation
Committee on Environment and Public Works
U.S. Senate
Washington, DC 20510

Dear Mr. Chairman:

Enclosed for insertion into the hearing record are EPA's responses to follow-up questions from the May 11, 1994 hearing on environmental tobacco smoke before the Subcommittee on Clean Air and Nuclear Regulation. I hope this information will be useful to you and members of the Subcommittee.

If you or your staff have any questions regarding this information, please contact Mary Nichols, Assistant Administrator for Air and Radiation at (202) 260-7400, or Gary J. Foley, Acting Assistant Administrator for Research and Development at (202) 260-7676.

Sincerely,

Robert W. Hickmott
Associate Administrator

Printed on Recycled Paper

RESPONSES TO QUESTIONS FROM SENATOR LIEBERMAN

Question 1. Dr. Gravelle of the Congressional Research Service testified that the statistical evidence does not appear to support a conclusion that there are substantial health effects of passive smoking. The EPA report concludes that the statistical evidence does support its conclusion that there are substantial health effects of passive smoking. What is the basis for EPA's contention that the statistical evidence supports EPA's conclusion?

Response: "Statistical evidence" is a misnomer; statistical methods are used to analyze and interpret epidemiologic or biologic evidence. The EPA's use of statistical methods to analyze these data follows scientifically accepted principles. EPA's Science Advisory Board peer-reviewed and approved of the statistical methods used. The results of these statistical analyses support all of EPA's conclusions on ETS. For example, in the analyses of the 30 epidemiologic studies on ETS and lung cancer, one of the many analyses showed that 9 out of the 17 studies which categorized risk by the amount of husbands' smoking were statistically significant, a result that would occur by chance with a probability of less than one-in-a-million.

Question 2. Dr. Gravelle testified that a threshold level for ETS exposure may exist and that, below this level, no harm from ETS exposure may occur. Is there any evidence that suggests that there is or is not a threshold level for ETS exposure? If so, please state that evidence? If the evidence suggests that there is a threshold level, please state what that threshold level of ETS exposure is.

Response: While individual tolerance levels vary, ETS causes both acute and chronic effects at typical environmental levels. The strongest evidence that there is no threshold of ETS for harm comes from studies showing the irritation and asthma exacerbation effects with short term exposures. The increased lung cancer risks observed in 17 out of 17 studies of women whose husbands smoked the most suggest that the threshold, if any, for lung cancer must be at levels below those typically observed.

Question 3. After the Science Advisory Board (SAB) conducted its first review of the EPA report, what recommendations did the SAB make? Did the SAB review the methodology that the EPA used in its report? If so, what were its conclusions?

Response: Enclosed is a copy of the SAB report dated April 19, 1991 from its December 1990 review of the EPA first external review draft dated May, 1990, and the SAB's recommendations and conclusions can be found therein (see Attachment 1). In brief, the SAB agreed that ETS is a Group A (known human) carcinogen but felt that a stronger case could be made. The SAB also recommended that the sections on the noncancer respiratory effects in children be strengthened. With respect to methodology, the SAB endorsed the use of meta-analysis for the lung cancer studies and recommended that the quantitative risk assessment be based on the epidemiology studies and not on a "cigarette-equivalents" approach.

Note: Some of the attachments submitted with these responses have been retained in committee files; some have excerpts appearing here; and others are printed in their entirety.

Question 4. What evidence other than epidemiologic evidence did EPA use to support its classification of ETS as a human lung carcinogen? Please explain how the other evidence supported EPA's conclusion.

Response: Please also see the response to Senator Faircloth's Question 64. EPA used a weight-of-evidence approach, which is fully detailed in the EPA report Chapters 3-6 and Appendices A-D (see Attachment 2). Chapter 1 of the EPA report provides an executive summary, which includes the development of the weight-of-evidence, in less technical language. Also, please see the attached "Setting the Record Straight: Secondhand Smoke is A Preventable Health Risk" (EPA-402-F-94-005) June 1994, especially pages 1-2, "Classification of Secondhand Smoke as a Known Human (Group A) Carcinogen" (see Attachment 3).

Question 5. Critics claim that the epidemiologic evidence that the EPA used to conclude that ETS is a human lung carcinogen is weak. As evidence of its weakness, they claim that the risk estimates, which express the statistical correlation for the rate of disease development contained in the epidemiologic data, are low. As a result, they argue that the data do not support EPA's conclusion that ETS is a human lung carcinogen. How do you counter this criticism?

Response: Please see the following responses in "Setting the Record Straight": page 3, "The Epidemiology Studies"; page 5, "Studies Completed Since Release of the EPA report"; and page 7, "The Congressional Research Service (CRS) Report" (Attachment 3).

Question 6. Critics claim that meta-analysis is a controversial statistical tool that should be used only when combining studies that have been conducted under similar conditions. What is meta-analysis? How do you counter the criticism regarding EPA's use of meta-analysis?

Response: Please see the response in "Setting the Record Straight" page 5, "Meta-analysis" (Attachment 3). Meta-analysis was used as an objective analytical technique to combine the results of all similar studies, with both positive and non-positive response, to provide an overall estimate of effect from spousal smoking. Furthermore, the SAB specifically endorsed the use of meta-analysis for the lung cancer database.

Question 7. Dr. Jane Gravelle has criticized the epidemiologic studies that EPA used to classify ETS as a human lung carcinogen, contending that they may contain nonsmoker misclassification and confounding factors. How did EPA control for the possible presence of nonsmoker misclassification and confounding factors when analyzing the 30 epidemiologic studies of ETS and lung cancer?

Response: For nonsmoker misclassification, the only source of upward systematic bias (i.e., a systematic bias that inflates the relative risk estimates) identified in the ETS lung cancer epidemiology studies, the relative risk estimate from each study was adjusted downward before testing for significance. The technique and the parameter estimates employed are presented in Appendix B of the EPA report (Attachment 2). For confounders please see the response in "Setting the Record Straight", page 6 - "Confounders" (Attachment 3). Also, please see EPA's attached response to Dr. Gravelle's report. The response is contained in a letter from Gary Foley of EPA to Dan Mulhollan, Director of the Congressional Research Service (Attachment 4).

Question 8. Please explain the difference between a one-tailed and a two-tailed statistical test. Why did EPA use a one-tailed test instead of a two-tailed test when analyzing the ETS and lung cancer epidemiologic data? Did EPA use a one-tailed test throughout the development of its report or did it switch to a one-tailed test during the report's development? Did the Science Advisory Board ever object to EPA's use of a one-tailed test? If so, on what grounds? Has EPA ever used a one-tailed test to classify a Group A carcinogen and, if so, for what substance? What role do confidence intervals play in statistical analysis? Is there any statistical difference between a one-tailed statistical test that has a 90% confidence interval and a two-tailed statistical test with a 95% confidence interval?

Response: Please see the response in "Setting the Record Straight", page 5 - "90% vs. 95% Confidence Intervals" (Attachment 3). See also the responses to Senator Faircloth's questions under the heading "Lowering the Confidence Interval."

Question 9. Critics contend that out of the 11 U.S. epidemiologic studies that EPA used in its weight of evidence analysis, not one reported a statistically significant increase in lung cancer that was associated with nonsmoker ETS exposure. How does EPA counter this criticism?

Response: Please see the response in "Setting the Record Straight", page 4-5, "The 11 U.S. Lung Cancer Studies" (Attachment 3).

Question 10. Critics claim that although EPA looked at 30 epidemiologic studies, it only statistically analyzed the 11 U.S. studies. Is that true? If so, please explain why EPA only statistically analyzed the 11 U.S. studies.

Response: This claim is not correct. The EPA statistically analyzed all 30 epidemiologic studies using a number of approaches. See especially Tables 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, 5-15, 5-16, and 5-17 of the EPA report (Attachment 2). Please also see the response in "Setting the Record Straight", page 4 - "The 11 U.S. Studies" (Attachment 3).

Question 11. Critics claim that EPA weighted selected data to support its conclusion that ETS is a human lung carcinogen. Did EPA weight the evidence and if so, please explain the weighting method that EPA used in its analysis.

Response: The EPA in its weight-of-evidence approach gave significant weight to the many studies showing that active smoking causes lung cancer; see Chapter 4 of the EPA report

(Attachment 2). It also gave significant weight to the 30 ETS epidemiology studies on spousal smoking and lung cancer. The specific weights given to each of the 30 individual studies are shown in the EPA report in Tables 5-9, 5-10, 5-16, and 5-17. The methodology used in the weighting procedure is presented in Appendix D. The methodology used in the individual study ranking or "tiering" procedure is presented in Appendix A. See also EPA's attached response to Dr. Gravelle's report (Attachment 4).

Question 12. You have testified that there are only two ways to effectively protect nonsmokers from involuntary exposure to environmental tobacco smoke: (1) prohibiting smoking indoors, and (2) restricting smoking to rooms that have a separate ventilation system. Why do you believe that prohibiting smoking indoors and restricting smoking to separately ventilated smoking rooms are the only options that effectively protect nonsmokers from involuntary ETS exposure.

Response: Simply separating smokers and nonsmokers within the same area may reduce exposure, but nonsmokers will still be exposed to smoke that is recirculated through the ventilation system or smoke drifting into nonsmoking areas.

Question 13. Critics claim that EPA's conclusion that ETS is a human lung carcinogen rests on the assumption that ETS and mainstream tobacco smoke are chemically similar. Is that true? If so, please explain why EPA contends that ETS and mainstream smoke are chemically similar.

Response: That ETS and mainstream smoke are chemically similar is part of the chain of reasoning that links the carcinogenic properties of mainstream smoke and ETS. Both mainstream smoke and ETS come from tobacco combustion. In fact, ETS is approximately 15% exhaled mainstream smoke.

Question 14. You stated in your testimony that the probability of the EPA's findings occurring by chance were very low. In one case, one-in-a-billion. Please explain these probabilities and why they support EPA's conclusion that ETS is a human lung carcinogen.

Response: Please see the response in "Setting the Record Straight", page 3 - "The Epidemiology Studies" (Attachment 3).

RESPONSES TO QUESTIONS FROM SENATOR FAIRCLOTH

The Brownson Study

Question 1. Who appoints the EPA's science advisory panel?

Response: The Science Advisory Board (SAB) is a Congressionally mandated Federal Advisory Committee. It presently has 100 Members and more than 300 Consultants serving on ten standing and several ad hoc committees. The Board holds approximately 50 to 60 public meetings each year, and reports directly to the Administrator of EPA.

The Administrator of EPA appoints all Members of the SAB. The staff director of the SAB appoints all Consultants.

The Science Advisory Panel (SAP) is a separate Federal Advisory Committee of EPA that deals with Federal Insecticide, Fungicide, and Rodenticide Act issues. It is housed in the EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS) and reports directly to the Assistant Administrator for OPPTS.

The SAP was created on November 28, 1975 pursuant to Section 25(d) of FIFRA, as amended by Public Law 94-140, Public Law 95-396, and Public Law 96-539. In accordance with this statute, the Panel terminated on September 30, 1981. It was reestablished by the Administrator pursuant to the Federal Advisory Committee Act (FACA) and Section 21(b) of FIFRA on April 25, 1983, and then reauthorized as a statutory committee by amendment to the FIFRA dated December 2, 1983 (Public Law 98-201). Under FIFRA (Public Law 98-201), the statutory Panel terminated on September 30, 1987. It was administratively reestablished on October 1, 1987 by the Administrator pursuant to FACA until reauthorized as a statutory Panel by amendment to the FIFRA, dated October 25, 1988 (Public Law 100-532).

Question 2. What funds including travel, reimbursement, salary, and or any other were paid by EPA to the science advisory panel?

Response: The SAB convened two public meetings of its Indoor Air Quality and Total Human Exposure Committee to review the risk assessment on passive smoking. The Committee was supplemented by Consultants for each meeting. Each meeting cost approximately $30,000 in travel, reimbursement, salary and other expenses, not including federal staff time.

Question 3. When will EPA complete its study of Electromagnetic Fields?

Response: The Agency published the draft report, "Evaluation of the Potential Carcinogenicity of Electromagnetic Fields," in 1990. The Agency is now working on a report summarizing the current scientific evidence on the health effects of electromagnetic fields. This report is expected to be available in February 1995. EPA is not updating the complete risk assessment at this time, because this would be duplicative of the efforts of other federal agencies that are currently conducting their own risk assessments on electromagnetic fields.

Question 4. If EPA finds that Electromagnetic Fields are a greater risk than ETS, will EPA withdraw its support of H.R. 3434 and S. 1680?

Response: EPA simultaneously addresses a wide range of environmental health risks of varying magnitude. We can perceive no logical relationship between ETS and electromagnetic fields that would suggest that EPA should withdraw support for the proposed legislation on environmental tobacco smoke should electromagnetic fields be determined to be a greater risk than ETS. EPA's support of H.R. 3434 and H.R. 1680 is based upon the fact that the proposed legislation would protect people from involuntary exposure to secondhand smoke in public buildings. Upon completion of its assessment of the health effects of exposure to electromagnetic fields, the Agency will determine what recommendations, if any, the Agency should make with respect to exposure to electromagnetic fields.

Question 5. Has the EPA calculated the relative risk associated with ETS including the Brownson data and the data from the other studies not included in the report? If so, please provide the results. In addition, would the agency please provide such calculations at a 95% confidence level?

Response: The Agency has not made such calculations for the reasons set forth in the response to Question 6 below.

Question 6. If not, why not? How difficult would it be to incorporate the numbers from the Brownson study (and any other studies omitted by the EPA) into the ETS risk assessment? If these are important issues, why wouldn't the EPA take the time to include all the data?

Response: The EPA included all studies published before the literature cutoff date for the final ETS report. In addition, studies published between the cutoff date and the publication of the final ETS report were analyzed to determine whether they were consistent with the EPA report's conclusions, and they were. These studies are addressed in an addendum included in the final report. Since the publication of the report, other studies, with similarly consistent conclusions, have been published (e.g., Liu et al., Am J Epidemiol 137:145-154, 1993; Fontham et al., JAMA 271:1752-1759, 1994; Chilmoncyzk et al., NEJM 328:1665-1669, 1993). The Agency does not believe that it is necessary to recalculate the pooled relative risk estimates every time a new study comes out. Such a recalculation based on the now-available studies would not alter the conclusions, which are based on the total weight of evidence, and would have a minimal impact on the final U.S. population risk estimate for lung cancer, which is based on two different approaches, not just on the pooled relative risk estimate.

Question 7. You have indicated that you wanted Americans to have the most accurate information with respect to ETS, yet you have not instructed your agency to incorporate the Brownson study and other data into a revised report despite repeated allegations that failure to do so demonstrates EPA's bias. Why won't EPA undertake and issue a thorough, revised report based on all existing data?

Response: New studies on numerous environmental pollutants are published constantly. The Agency would consider revising a risk assessment if new studies appeared to indicate a substantial change. In the case of ETS, however, none of the recent lung cancer studies would alter the fundamental conclusion that ETS is a known human carcinogen. If any section were to be revised, it might be more appropriate to revise the chapters on noncancer respiratory effects, because new studies in this area have produced results that might increase the Agency's concerns on the respiratory health effects of ETS in children, especially with respect to sudden infant death syndrome, asthma induction, and long-term impairment of lung function.

Also of concern to the Agency is the mounting evidence linking ETS to heart disease. Published articles have linked ETS to as many as 40,000 heart disease deaths annually, and recent studies have shown both mechanism links in animals and dose-response relationships in human workplace environments.

Question 8. Would you please provide me with copies of any and all internal EPA materials and documents that concern the agency's evaluation of the Brownson and Alavanja studies and indicate which documents or data support your statement that these studies would have no impact on the EPA's risk assessment of ETS.

Response: The published studies themselves are the only relevant documents that EPA has.

Question 9. Are EPA employees authorized to testify as witnesses in state proceedings on IAQ or indoor smoking?

Response: EPA employees are permitted to act as witnesses in state proceedings with the approval of EPA management.

Question 10. The Deputy Director of the Indoor Air Division at the EPA recently suggested that ETS is only one component of interest to the EPA and is not the primary focus of the indoor air program. Robert Axelrad, the Director of EPA's Indoor Air Division, has stated that although ETS is important, it is not the only IAQ constituent of concern. Are these statements correct? Describe EPA's current indoor air program.

Response: These statements are correct. While media and tobacco industry attention has created the appearance of an overwhelming emphasis on environmental tobacco smoke by EPA, this impression is not an accurate reflection of the balance of EPA's indoor air program. EPA conducts a comprehensive program to better understand the indoor air pollution problem and to take steps to reduce people's exposures to all indoor air contaminants. The program addresses indoor air pollutants of all types, as well as total building issues, such as sick building syndrome. Enclosed are materials prepared by the Indoor Air Division which provide a more accurate picture of the Agency's indoor air program activities (see Attachment 5).

Question 11. Are there in fact many important IAQ constituents of potential concern? Should all of these be equally included in any "comprehensive" indoor air quality proposal? If not, why not?

Response: A "comprehensive" indoor air quality program should encompass both a building system approach and a pollutant specific approach, although it is not necessarily true that each individual contaminant should receive precisely the same degree of attention. EPA sets a high priority on improving the way in which buildings are designed and operated. This emphasis on a buildings approach holds the most promise for addressing all of the factors -- including those related to the ventilation system as well as sources of individual pollutants -- that affect indoor air quality. EPA also strongly believes that it must aggressively utilize its combined statutory authorities to identify specific pollutants that present direct health risks to the indoor environment and to use a variety of means to reduce their levels indoors.

Question 12. The EPA's activities regarding ETS, as well as your own, have received a lot of publicity recently. Can you provide examples of how you are aggressively pursuing other indoor air constituents besides ETS?

Response: The indoor air pollutants that are currently receiving significant Agency attention, in addition to environmental tobacco smoke, include radon, asbestos, toxic substances, lead, pesticides, and indoor air pollutants from drinking water, which are discussed in more detail below. In addition, the Indoor Air Division has funded or published a number of documents that address biological contaminants, combustion gases, and other indoor air pollutants.

- Radon: The Indoor Radon Abatement Act of 1988 (Title III of TSCA) established a national goal of achieving indoor levels of radon which are no greater than outdoor levels. EPA has undertaken a range of activities directed toward this goal, including revising public information materials, providing financial and technical assistance to States, developing and encouraging the adoption of radon resistent building practices, establishing training centers, operating industry proficiency programs, conducting studies in schools and Federal buildings, and performing mitigation research in different building types.

- Asbestos: Title II of the Toxic Substances Control Act (TSCA), the Asbestos Hazard Emergency Response Act (AHERA) requires EPA to establish a regulatory framework for addressing asbestos in schools. The Agency has set standards for state accreditation of personnel involved in asbestos management or abatement in school buildings and will extend accreditation requirements to those who inspect or abate asbestos in public and commercial buildings. EPA is also involved in a range of outreach, grant, and technical assistance activities in these areas.

- Toxic substances: TSCA grants EPA broad authority to control chemical substances and mixtures that present an unreasonable risk of injury to health and the environment. EPA has authority to require testing of chemical substances and mixtures; regulate hazardous chemical substances and mixtures by prohibiting or restricting their manufacture, processing, distribution, and disposal; review new chemicals and their intended uses; and impose labeling or notification requirements. TSCA has been used to regulate asbestos, and the Agency is now evaluating groups of chemicals in selected use categories for their effect on people in indoor environments.

- Lead: EPA is working to develop a comprehensive strategy to address lead exposures and to develop effective lead testing and abatement procedures.

- Pesticides: FIFRA authorizes EPA to control pesticide exposures by requiring that any pesticide be registered with EPA before it many be sold, distributed, or used in this country., EPA is evaluating the health impacts of indoor products including insecticide sprays, termiticides, and wood preservatives.

- Indoor air pollutants from drinking water: The Safe Drinking Water Act (SDWA) authorizes EPA to set and enforce standards for contaminants in public water systems to protect against both health and welfare effects. EPA sets standards for volatile organic compounds that can enter the air through volatilization from water used in a residence or other building. EPA is also developing standards for radon in drinking water.

In addition, the Indoor Air Source Characterization Project is a multi-year, intra-agency project, jointly led by the Office of Radiation and Indoor Air, the Office of Pollution Prevention and Toxics, and the Office of Research and Development. The purpose of this project is to determine those classes of products which are major contributors to indoor air exposures and risks, and to take actions, as necessary, to reduce exposures and risks.

Question 13. Is EPA working with OSHA on ETS or IAQ issues? Please explain and fully describe all of EPA's involvement at OSHA.

Response: The activities of more than 20 Federal agencies that have responsibilities associated with indoor air quality (either through their own statutory responsibilities or because they are major property owners) are coordinated through the interagency Committee on Indoor Air Quality (CIAQ). The CIAQ meets on a quarterly basis to exchange information. EPA and OSHA are two of the five co-chair agencies, with the Consumer Product Safety Commission, the Department of Energy, and the National Institute for Occupational Safety and Health. EPA has, of course, provided OSHA with information developed by EPA on an ongoing basis for several years. EPA staff scientists also interact with OSHA scientists on ETS issues.

Question 14. Did EPA help draft OSHA's proposed rulemaking on indoor air quality published in the Federal Register on April 5, 1994? Explain in detail.

Response: EPA did not help draft OSHA's proposed rulemaking on indoor air quality and environmental tobacco smoke. EPA was apprised of OSHA's intent to issue a proposed rule well in advance of its release. OSHA's representatives to the quarterly meetings of the interagency Committee on Indoor Air Quality provided general status reports in the months prior to the proposal, and made it clear that a workplace smoking regulation, either alone or in conjunction with a more comprehensive indoor air quality regulation, was under serious consideration. At the time the proposal was sent to OMB, EPA was given an opportunity to review the proposal. EPA also submitted comments to OSHA for OSHA's September 1994 hearings on the proposed rule.

An EPA employee was detailed to OSHA for several months, at OSHA's request, to assist in the development of portions of the OSHA proposal. This person, however, does not represent EPA in any official capacity, either as a liaison or as a technical or policy representative.

Science Advisory Committee Required by the Radon Gas and Indoor Air Quality Research Act

[Note: in responses to Questions 16-19, current members are indicated with an asterisk.]

Question 15. Name the Advisory Committee to be comprised of "individuals representing the states, the scientific community, industry, and public interest organizations" required by [Sec.] 403(c) of the Radon Gas and Indoor Air Quality Research Act.

Response: The "Indoor Air Quality and Total Human Exposure Committee" is the Advisory Committee required by the radon act. This Committee was formed in 1986 as a result of that legislation.

Question 16. Name the individuals on that Committee which have and presently represent the states.

Response: Dr. Jerome Wesolowski-California (Note: Dr. Wesolowski died on January 1, 1994.) Dr. Robert Hazen-New Jersey*

Question 17. Name the individuals on that Committee which have and presently represent the scientific community.

Response: Dr. Morton Lippmann-New York University*; Dr. Joan Daisey-Lawrence Berkeley Lab*; Dr. Jonathan Samet-University of New Mexico*; Dr. Victor Haties-University of Rochester; Dr. Jan Stolwijk-Yale University; Dr. Maria Morandi-University of Texas*; Dr. Paul Lioy-R.W. Johnson School of Medicine*, Dr. Brain Leaderer-Yale University School of Medicine*; Dr. Timothy Larson-University of Washington*

Question 18. Name the individuals on that Committee which have and presently represent industry.

Response: Dr. James Woods-Honeywell (then Virginia Polytechnic Institute and State University); Mr. Roger Morse-ENTEK*; Dr. Paul Bailey-Mobil Oil*

Question 19. Name the individuals on that Committee which have and presently represent public interest organizations.

Response: Ms. Mary Ellen Fise-Consumer Federation of America; Mr. Ronald White-American Lung Association*

Exposure

Question 20. Administrator Browner, you state that with ETS, you are able to see a consistent increase in human cancer risk at "typical environmental levels." What, specifically, is the "typical environmental level" of ETS? Please provide all EPA documentation which relates in any way as to how that level was derived.

Response: The exposure information is documented in Chapter 3 of the EPA report (Attachment 2). Increases in lung cancer are observed in epidemiology studies where spousal smoking, as determined by questionnaire responses, serves as a surrogate measure of ETS exposure. Chapter 3 documents the correlation between questionnaire responses, environmental exposure measurements in the home, and biomarker levels of exposure. The chapter also documents that home exposure levels are generally comparable to ETS levels in other environments where smoking occurs, such as various workplaces and public places. Hence, these exposure levels are typical of those that nonsmokers frequently encounter in their general environments.

Question 21. How does the EPA numerically define this level? What data does EPA rely upon?

Response: The relevant exposure data are documented in Chapter 3 of the EPA report (Attachment 2). There is no numerical definition of this level; "typical environmental levels" encompasses the range of ETS levels that nonsmokers are typically exposed to in common environments where smoking occurs.

Question 22. Does the EPA regard its exposure assessment guidelines as important? If so, explain. Does the EPA regard them as binding?

Response: Yes, the guidelines are important for providing a general framework or guidance for conducting exposure assessments. No, they are not legally binding. See also responses to questions 58-64.

Childhood Morbidity Estimates

Questions 23 and 24. How did the EPA arrive at these estimates and how do you claim to support these estimates? Please provide any and all documents which support these estimates.

Response: The derivations of these estimates and references for all documents used in the derivations are documented in Chapter 8 of the EPA report (Attachment 2).

Lowering the Confidence Interval

Question 25. In EPA's view, what is the purpose of a confidence interval?

Response: A confidence interval is an estimate of the variability in the observations under the assumption that the data have a specified distribution.

Question 26. How many of the 30 studies relied upon by the EPA used a 95% confidence interval? How many of the U.S. studies used a 95% confidence interval?

Response: The EPA relied upon hundreds of studies to make its determination of ETS and lung cancer and hundreds more to make its determination on noncancer respiratory effects. Eighteen of the 30 epidemiology studies of ETS and lung cancer and 8 of the 11 U.S. studies used a 95% confidence interval.

Question 27. What would be the effect of lowering the confidence interval from 95% to 90%? What reasons, if any, would justify such a change?

Response: There would be no effect on the EPA conclusions on ETS being a human lung carcinogen. A 90% confidence interval is an alternative depiction of the variability about the estimate; there is no profound "effect" of using one versus the other. The confidence interval in the EPA risk assessment is more readily consistent with the one-tailed statistical test at the $p=0.05$ significance level that was used for statistical significance testing of the ETS lung cancer epidemiology studies. Such a one-tailed test is a standard statistical methodology used when there is prior evidence that if there is an effect of an agent, the effect is likely to be in one specific direction. In the case of ETS, the prior evidence was the well-established causal association between active smoking and lung cancer coupled with the chemical similarity between mainstream smoke and ETS. This prior evidence supported the hypothesis that if ETS were also associated with lung cancer, it would be in a similar causal manner versus a negative association.

The EPA risk assessment portrays 95% confidence intervals for the estimates of noncancer respiratory effects mainly in children. These are consistent with the two-tailed statistical significance tests used for these effects, where there was less prior evidence of associations with active smoking.

Question 28. Did the EPA ever perform the meta-analysis of U.S. lung cancer studies at a 95% confidence interval? If not, why not? If so, please provide copies of any and all EPA documents relating to such calculation.

Response: Yes. The pooled estimated relative risk of U.S. studies is 1.25 (95% confidence interval 1.03, 1.52) unadjusted for background, presented in the first external draft, May 1990, pages 4-24.

Question 29. Is it not correct that when EPA lowered the confidence interval to 90%, they doubled the chance of being wrong? If you maintain this is not correct, please explain.

Response: Since the confidence intervals are not statistical tests, they do not influence the chances of "being wrong". Use of a one-tailed statistical test does increase the sensitivity of the test to detect a positive association, for an individual study. However, the EPA's conclusions are based on the total weight of evidence and not an individual study. The total weight of evidence, including the **consistency** of the results from the **30** epidemiology studies of ETS and lung cancer, especially the increased risks uniformly observed in the highest exposure groups and the positive dose-response trends, provides very strong evidence of a causal association.

Question 30. Didn't an article in Science attribute to Jennifer Jinot, one of the authors of EPA's report, the statement that "she and her colleagues engaged in some fancy statistical footwork" in preparing the ETS report? How does the EPA interpret this statement? Isn't the statement in fact true?

Response: The Science article did not attribute that statement to Jennifer Jinot. The only statement attributable to her is the phrase "total weight of evidence" that appears in quotation marks in the article. The phrase "fancy statistical footwork" does not appear in quotation marks in the article, and is the reporter's own journalistic representation of the comprehensive and rigorous statistical analyses described to him.

Question 31. Why did the EPA find it necessary to change the confidence level set by the vast majority of the authors of the original studies that the EPA gathered data from between the first draft of the risk assessment on ETS and the final document?

Response: Some of the authors of the original 30 papers on lung cancer and ETS used 95% confidence intervals, some used 90% confidence intervals, and some did not report confidence intervals at all. For consistency, the EPA report provides confidence intervals with the same confidence level for all of the studies. The EPA changed the confidence interval for the overall ever-vs-never comparison display between the first and second drafts of the risk assessment because the 90% confidence interval was more readily comparable to the one-tailed statistical significance test used in **both** drafts as well as in the final report. This change in confidence intervals had **no** effect on statistical significance testing of the studies.

Question 32. What reasons can you provide why the EPA would not recalculate their point estimate using a 95% confidence interval?

Response: 95% confidence intervals are not used to calculate point estimates. The computations and the concepts are totally different.

Question 33. If the estimate using the 95% confidence interval would differ from the estimate using a 90% confidence interval, what would that say about your original estimate?

Response: As stated in responses to the previous questions, the point estimate would not change at all.

Question 34. Your agency has stated that it was recommended by the scientific community that you should use a 90% confidence interval because it was "appropriate for this data". Who recommended the change and on what basis? Please provide any documents which contain recommendations for such a change.

Response: The EPA used one-tailed statistical significance tests for the lung cancer epidemiology studies, which is standard statistical methodology in certain circumstances (See response to Question 27 above), such as with ETS epidemiology and lung cancer.

Question 35. What are the differences in the data between the EPA's 1990 draft of the ETS risk assessment and the 1992 draft which EPA believes supports the change in the appropriate confidence interval?

Response: There are no differences in the data suggesting a change. The authors of the EPA report realized that the 95% confidence intervals used in the first external review draft were not directly comparable to the one-tailed statistical significance test that was used throughout the entire development of the risk assessment.

Question 36. Doesn't the EPA normally use a 95% confidence interval when conducting risk assessments? Please identify each risk assessment ETS has conducted, and for each, please state the confidence interval used by EPA.

Response: The EPA uses both 90% and 95% confidence intervals when conducting risk assessments. The ETS risk assessment uses both 90% and 95% confidence intervals. There are far too many risk assessments to identify individually. However, most use "a plausible upper limit unit risk estimate" or "potency factor" which is derived from the upper limit of the 90% confidence interval.

Question 37. How many of the EPA risk assessments designating substances as Group A carcinogens used a 95% confidence interval? Please list each risk assessment conducted by EPA which applied a carcinogen classification under the EPA's carcinogen risk assessment guidelines.

Response: Please see the response to Question 36 above and the Table of Group A Carcinogens in the response to Questions 79 and 81. The enclosed CD-ROM (see Attachment 6) contains the risk assessments for these carcinogens, with the exception of radon, for which the technical support document (see Attachment 7) is provided. Please note that when terms like "95% upper-limit risk" or "95% UCL" (upper confidence limit) are used (for example, the Health Assessment Document for Nickel and Nickel Compounds, EPA/600/8-83/012FF, page 8-209), they are based on 90% confidence intervals. In the Technical Support Document for the 1992 Citizens Guide to Radon (EPA-400-R-02-011, May 1992), 90% confidence intervals are presented on pages 2-23, 2-30, and 2-31, for example.

Question 38. On what basis does the EPA defend itself against the criticism that it predetermined the end result of the risk assessment on ETS?

Response: EPA did not predetermine the end result of the ETS risk assessment. The risk assessment was developed over a four-year period, undergoing many revisions and two external review drafts, and the conclusions were based on the total weight of scientific evidence. In fact, the conclusions on noncancer respiratory effects changed substantially between the first and second drafts.

General Risk Assessment Questions

Question 39. What is EPA's definition of a health risk assessment and what does an EPA health risk assessment contain?

Response: EPA adheres to the definition of risk assessment provided in the National Research Council's 1983 report "Risk Assessment in the Federal Government: Managing the Process." On page 18 of that report, risk assessment is defined as "the characterization of the potential adverse health effects of human exposure to environmental hazards," and is further described as consisting of "several elements: description of the potential adverse health effects based on an evaluation of results of epidemiologic, clinical, toxicologic, and environmental research; extrapolation from those results to predict the type and estimate the extent of health effects in humans under given conditions of exposure; judgments as to the number and characteristics of persons exposed at various intensities and durations; and summary judgments on the existence and overall magnitude of the public health problem. Risk assessment also includes characterization of the uncertainties inherent in the process of inferring risk."

Question 40. Why is a risk assessment conducted by EPA? What is the purpose of Carcinogen Risk Assessments prepared by the Agency?

Response: The EPA Guidelines, following the National Research Council's 1983 report "Risk Assessment in the Federal Government: Managing the Process," make a clear distinction between "risk assessment" (as defined in the previous response) and "risk management," which constitutes the process of decision about whether or how much to control future exposure to the suspected toxic agent based on information from risk assessment together with social, economic, legal, and political factors. That is, risk assessment is a tool that is used to understand and characterize the potential risks that may be associated with exposure to an environmental agent, and the development of this understanding is separate and distinct from any regulatory action that may be taken. Accordingly, EPA uses risk assessment whenever characterization of an agent's potential risks is important to its fulfilling its multifaceted mission. This includes supporting regulatory action, but also extends to planning and conducting research, screening chemicals new to commerce, and developing and providing information on potential health risks, such as the Agency is mandated to do for potential health effects from indoor air.

Question 41. Isn't it true that EPA's guidelines on risk assessment are intended for use in assessing risks subject to regulation under EPA enabling statutes?

Response: Yes, but not solely for such use, as outlined in the answer to the previous question. Risk assessment is a tool for characterizing potential health risks; it is therefore used in all parts of the Agency's mission that call for such characterization.

Question 42. What factors led to EPA's decision to conduct a Carcinogen Risk Assessment? What factors led to EPA's decision to conduct a risk assessment on ETS and who made that decision?

Response: EPA performs health risk assessments to assist in deciding whether a potential risk exists (screening assessment) or to support fuller characterization of an identified potential risk (full assessment). Usually the decision to proceed to full assessment is based on a program decision that the potential exposure from a pollutant is of a magnitude that justifies spending the resources to characterize the potential risk. In the case of ETS, the Office of Air and Radiation (OAR) already had an indication of the potential magnitude of the problem from both the 1986 National Academy of Sciences and the 1986 U.S. Surgeon General's reports describing ETS as a risk for lung cancer and other respiratory disorders. In 1988, OAR requested that the Office of Research and Development (ORD) perform an assessment that would incorporate data published since the previous reports and more fully characterize the exposure and potential risks. The assessment was done by ORD under an agreement between the Offices.

Question 43. What statutory authority does the EPA have to conduct carcinogen risk assessments? Where does EPA get its authority to conduct risk assessments?

Response: Numerous statutes authorize EPA to conduct regulatory programs, and as in this case, informational programs that involve assessments of risk to public health, including carcinogenic risks.

Question 44. Is EPA's authority to conduct risk assessments found in more that one statute? What statutes authorize carcinogen risk assessments? Isn't it true that Congress has directed EPA to conduct risk assessments of certain substances or as to certain risks? Is it agency policy for EPA to conduct risk assessment with respect to substances or risks over which it has not been delegated authority by Congress?

Response: See response to question 43. All statutes that authorize EPA to conduct regulatory or informational programs regarding public health risks associated with exposure to pollutants in environmental media or in food or, in this case, in indoor air, authorize the conducting of risk assessments. Congress usually specifies the problem area, such as water, food, or indoor air; it rarely specifies a substance, and when it does, it does so as an addition to those the Agency identifies. EPA conducts its risk assessments in accordance with Congressional authorization and appropriation language.

Question 45. Do you maintain that EPA has unfettered authority to conduct risk assessments whenever it wants?

Response: See responses to questions 42-44.

Question 46. Do you claim that EPA has inherent authority to perform risk assessments of substances or risks which are not addressed by Congress?

Response: See responses to questions 42-44.

Question 47. Assuming that Congress specifically exempts a substance from regulation, does EPA have authority to determine that the exempted substance ought to be the subject of an EPA risk assessment and act accordingly?

Response: Whether Congress specifically exempts a substance from regulation is an issue distinct from whether Congress has authorized EPA to conduct a risk assessment of that same substance. The risk assessment of ETS was conducted pursuant to Congressional authorization.

Question 48. What process does EPA have in place to assure that the agency has statutory authority to conduct activities with respect to a particular substance or risk?

Response: Conducting activities in accord with existing law is the responsibility of national program managers, with the advice of Agency counsel as needed.

Questions 49 and 50. Much of the activity conducted by EPA is conducted by non-lawyer professionals who may not understand the concepts of delegated authority and separation of powers. What process does EPA have in place to assure that these non-lawyer professionals do not initiate and carry out activity which has not been authorized by Congress? What assurances do the American taxpayers have the EPA is not running amuck, "protecting the environment" based upon personal values rather than legal authority?

Response: EPA staff and management closely adhere to the parameters provided by statute and regulation. The structure and management of the Agency ensures that unauthorized activities do not take place. In addition, some Agency regulatory and policy actions are reviewed within the Administration through the Office of Management and Budget.

Question 51. Would you agree that proper use of EPA's risk assessment guidelines requires a classification based on those factors included in the guidelines? Alternatively, is a determination that a substance is a carcinogen followed by suggested revisions to the guidelines in order to support the determination on acceptable use of the guidelines?

Response: EPA's Guidelines for Carcinogen Risk Assessment outline a general approach based on stated principles, but they recommend that each assessment be done according to the scientific approach most appropriate for the information at hand. They state (51FR33993) "These Guidelines describe the general framework to be followed in developing an analysis of carcinogenic risk and some salient principles to be used in evaluating the quality of data and in formulating judgments concerning the nature and magnitude of cancer hazard from suspect carcinogens. It is the intent of these Guidelines to permit sufficient flexibility to accommodate new knowledge and new assessment methods as they emerge....These Guidelines provide general directions for analyzing and organizing available data." The Guidelines go on to state "It is also recognized that there is a need for new methodology that has not been addressed in this document in a number of areas....Guidelines will be revised whenever appropriate." This guidance makes clear that risk assessments should address the issues raised in the Guidelines, but that no specific or rigid requirements are imposed. Indeed, they require (51FR33992) that "risk assessments will be conducted on a case-by-case basis, giving full consideration to all relevant scientific information...and use the most scientifically appropriate interpretation to assess risk." In the course of this process, some case-specific issue may be raised that could usefully be addressed in a more general context in revised or updated guidelines; the current Guidelines say that the most appropriate use of the information should be made in the agent's risk assessment, while encouraging the raising of the more general point for consideration in future guidelines revisions.

Question 52. What specific legal authority did EPA have to conduct a risk assessment of electromagnetic fields?

Response: Under the authority of the Atomic Energy Act, the Agency published the draft report, "Evaluation of the Potential Carcinogenicity of Electromagnetic Fields" in 1990.

Question 53. What legal authority did EPA have to conduct a risk assessment of diesel fuel?

Response: EPA published a draft risk assessment of diesel fuel in July 1990, under the authority of Sec. 202 of the Clean Air Act Amendments. An updated version is expected to be completed later this year. Under Sec. 206 of the Clean Air Act Amendments, EPA published "Motor Vehicle Related Air Toxics Study" in April 1993, which includes a chapter on diesel fuel.

Question 54. What specific legal authority did EPA have to conduct a risk assessment of radon?

Response: The following provisions give EPA authority to assess health risks from radon: 15 U.S.C. 2665(a)(4); 15 U.S.C. 2667(a)(5)(A); 15 U.S.C. 2669(d)(l)(A); the Superfund Amendments and Reauthorization Act of 1986 (Sec. 118(k)).

Question 55. What specific legal authority did EPA have to conduct a risk assessment of environmental tobacco smoke?

Response: EPA may conduct a risk assessment of ETS pursuant to Congressional authority. This authority includes the Radon Gas and Indoor Air Quality Research Act of 1986 (Title IV of the Superfund Amendments and Reauthorization Act).

Question 56. Does EPA have statutory authority to regulate any aspect of indoor air? If so, explain.

Response: EPA does not have statutory authority to regulate indoor air pollution.

Question 57. Assuming Congress has not delegated any authority to EPA to perform regulatory activity with respect to a substance or risk, where would EPA obtain authority to perform a risk assessment of such substance or risk?

Response: Authorities conveyed by Congress to EPA do not narrowly apply only to regulatory activity. For example, the Radon Gas and Indoor Air Quality Research Act of 1986 does not convey to EPA any regulatory authority but does convey authority to conduct a wide range of research and information dissemination activities with respect to indoor air pollution.

Carcinogen Risk Assessment Guidelines and Exposure Assessment Guidelines

Question 58. Isn't it true that EPA has adopted its own risk assessment guidelines entitled "Guidelines for Carcinogen Risk Assessment"?

Response: EPA finalized and published its Guidelines for Carcinogen Risk Assessment in 1986 (51FR33992). These are stated to follow the general precepts of the National Research Council's 1983 report "Risk Assessment in the Federal Government: Managing the Process" and the Office of Science and Technology Policy's "Chemical Carcinogens: Review of the Science and its Associated Principles" (50FR10372).

Question 59. Isn't it also true that EPA has adopted exposure assessment guidelines to govern EPA's preparation of exposure assessments in risk assessments?

Response: EPA finalized and published a revision of its 1986 exposure assessment guidelines in 1992 (57FR22888).

Question 60. Wouldn't you agree the risk assessment guidelines and exposure assessment guidelines provide detailed guidance on how to conduct such assessments?

Response: No. The guidelines provide a general framework and establish some guiding principles, but they specifically mandate a flexible approach using methods that are most scientifically appropriate to the case at hand. Depending on the specific topic, the guidelines may be more or less specific as to the suggested or default approach that is usually considered appropriate, but in most cases details are not specified in the guidelines documents.

Question 61. Wouldn't you agree that EPA thoroughly addressed these types of assessments in those guidelines?

Response: The EPA guidelines definitely address risk assessment and exposure assessment methods, doing so in the depth and thoroughness appropriate for general, flexible guidelines. At the same time, the guidelines explicitly recognize that they cannot be utterly comprehensive and all-encompassing, as cited in the response to Question 51 above.

Question 62. Isn't the EPA clearly required to follow these guidelines in conducting risk assessments and exposure assessments?

Response: Guidelines, as distinguished from "legislative" regulations promulgated under notice and comment procedures, are nonbinding by nature. For instance, the carcinogen guidelines (51FR33992) state, "These Guidelines are not major rules as defined by Executive Order 12291, because they are nonbinding policy statements." As such policy statements, however, the guidelines mandate flexibility and the use of the most appropriate methodology based on case-by-case judgment. "Following the guidelines" means making such judgments, following sound scientific principles. It also necessarily involves a judgement as to whether there should be a departure from the substantive terms of the guidelines in that particular case.

Question 63. Isn't the public entitled to expect that EPA will follow its own guidelines in conducting risk assessments and exposure assessments?

Response: Yes, the public entitled to expect that each case be considered carefully on its particular merits and that methods judged most appropriate to the case at hand be used. The public is entitled to expect that consistent principles guide this judgment, based on the considered opinions of the scientific community and explicitly laid out in guidance documents that have undergone public comment and peer review. The guidelines aim at setting out such principles; Science Advisory Board review of risk assessments conducted under the guidelines ensures that the framework and general principles articulated therein are followed, and that the specific analyses conducted in particular risk assessments are consistent with these principles and the appropriate interpretation of the particular scientific data at hand.

Question 64. Do you believe EPA followed these guidelines in its ETS risk assessment? If so, why do you believe this?

Response: Yes, the EPA followed these guidelines. For example, the Agency conducted a weight-of-evidence analysis of the available information, including evidence from epidemiology studies, animal bioassays, genotoxicity studies, and exposure measurements, as recommended in the guidelines.

Home vs. Workplace Exposure Data

Question 65. Administrator Browner, you claim that the epidemiological studies are the most controlled when studying home exposure. Please explain that position.

Response: Spousal smoking represents the best single indicator of ETS exposure over the decades it may take to develop lung cancer. Workplace exposures are generally less stable over time because workers frequently change jobs or worksites, and coworkers frequently change. Workers may also be exposed to high levels of other lung carcinogens, which could affect the ability to study ETS' lung cancer effects. Furthermore, the epidemiology database on spousal smoking is much larger than that on workplace ETS exposure.

Question 66. Did any of the studies relied upon by EPA in its ETS risk assessment actually measure levels of ETS in the home?

Response: Levels of nicotine, respirable suspended particulates, and other components of ETS were actually measured in homes. Chapter 3 of the ETS report deals specifically with measurement and assessment of ETS exposure, and reviews a large amount of data on (components of) ETS levels in the home as well as in other indoor or enclosed environments.

Question 67. Has the EPA conducted any ETS exposure research in the workplace? If so, explain.

Response: EPA has not sponsored studies with a dedicated or primary focus on workplace exposure with one exception which has been published as Mattson, M.E. et al., Passive Smoking on Commercial Airline Flights. Journal of the American Medical Association, 261 (6): 867-872 (1989). In this study, five passengers and four flight attendants were studied on four commercial flights for approximately four hours duration. Air nicotine levels, urinary cotinine levels, and self-reports of exposure were assessed.

Coincident to research on other aspects of indoor air quality and/or health effects, there are a few studies focused on general indoor/outdoor contaminants such as particulates or PAHs for which knowledge of the presence or absence of tobacco smoke was desired and a workplace setting was one of several settings encountered. The rigorous correlation of these contaminants with tobacco smoke was not done. Rather, an occasional measuring for nicotine was done to verify that smoke was present and thus contributing, or not, to the contaminants of primary interest. One such study involved following individuals over a 12-hour period in Riverside, California with part of the study measuring particulates and part measuring PAHs and phthalates. The references for these studies are:

> Particle Total Exposure Assessment Method (P-TEAM): Riverside California, Pilot Study Volume 1, Pellizzari, E.D. et al., EPA/600/SR-93-050, May 1993.
>
> Monitoring of Phthalates and PAHs in Indoor and Outdoor Air Samples, Riverside California, P-TEAM Volume 2, Jointly funded project by EPA and California Air Resources Board, published by California Air Resources Board under contract #A933-114, December 1992.

Question 68. Does EPA have any actual exposure data to determine whether exposure to ETS is greater in the home or in the workplace?

Response: Yes. These data are reviewed in Chapter 3 of the ETS report (see Attachment 2).

Confounding

Question 69. Can you give me the EPA's definition of confounding or confounding factors?

Response: Confounding, as used in describing factors in epidemiologic studies, is a general term, not a specific EPA term. The definitions are:

1. A situation in which the effects of two processes are not separated. The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome.

2. A relationship between the effects of two or more causal factors as observed in a set of data, such that it is not logically possible to separate the contribution that any single causal factor has made to an effect.

3. A situation in which a measure of the effect of an exposure on risk is distorted because of the association of exposure with other factor(s) that influence the outcome under study.

A confounding factor is one which must be associated with both the exposure under study and the outcome disease under study.

Question 70. Why did you say in your testimony that you "disagree" with the position that confounding might play a role in the risk purportedly associated with ETS? Explain.

Response: The EPA report did examine the available data for six potential confounders such as occupation, dietary factors, and history of lung disease, and concluded that none was likely to explain the lung cancer increases seen in the studies.

Question 71. What sort of exposure or behaviors can EPA say have been associated with an increased risk of lung cancer in nonsmokers?

Response. In EPA's purview, the list of known human lung carcinogens includes arsenic, asbestos, bis (chloromethyl)-ether, chromium VI, coke oven emissions, ETS, nickel and radon. There is also suggestive evidence of lung carcinogenicity in many compounds from animal studies. Although not officially on the EPA list, active smoking is generally recognized as the largest risk factor for lung cancer.

Question 72. Have scientific studies shown that these potential risk factors might vary between smokers and nonsmokers, and also between persons living in smoking versus nonsmoking households?

Response: Some of the epidemiology studies of ETS and lung cancer have examined some potential risk factors for lung cancer and have found no evidence that these factors are confounding the association between ETS and lung cancer. Occupational levels of asbestos and radon have been shown to have synergistic (multiplicative) effects on risks for lung cancer in smokers. Nickel is present in tobacco smoke, so interaction is difficult to ascertain. The other substances listed above have been determined to be lung carcinogens based upon high (occupational) levels of exposure rather than environmental (home) levels, whether in homes of smokers or non-smokers.

Question 73. It is not only conceivable, but indeed very probable that confounders of the claimed ETS-lung cancer relationship do exist?

Response: The EPA report did examine the available data for six potential confounders, i.e., history of lung disease, family history of lung disease, heat sources for cooking or heating, cooking with oil, occupation, and dietary factors and concluded that none was likely to explain the lung cancer increases seen in the studies.

In addition, consistency of results across different countries (including dose response) where lifestyle factors such as diet, vary, argues against confounding. For example, a high fat diet is considered to be a potential confounding factor, but the studies from Japan, where dietary fat intake is among the lowest in the world, show a strong dose-response relationship for secondhand smoke and lung cancer.

The 1994 Fontham et al. study controlled for diet and other potential confounders, including the high risk occupational exposures, and concluded, "These observations indicate that the strong association in this study between adult secondhand smoke exposure and lung cancer risk cannot be attributed to any likely confounder."

Question 74. Why does EPA insist that a single confounder must be found that applies to all the spousal smoking studies? Won't different factors be relevant in different populations both around the world and within the United States?

Response: EPA agrees that there may be different confounding factors in different populations both around the world and within the U.S. EPA has never insisted that a single confounder must be found across all the spousal smoking studies.

Question 75. Describe how the EPA accounted for confounders in the ETS risk assessment?

Response: Please see the attached "Setting the Record Straight", page 6, "Confounders" (Attachment 3), and the EPA report, sections 5.4 for lung cancer and 8.1 for noncancer respiratory effects (Attachment 2).

Group A Carcinogens

Question 76. Ms. Browner, you testified that ETS is the sixteenth agent to be classified as a Group A carcinogen by the EPA, yet Mr. William Farland of EPA testified in 1993 before Congress that there were ten other agents besides ETS so classified. Is there an explanation for this inconsistency?

Response: The number of EPA Group A carcinogens depends to some extent on how they are counted. For example, benzidine and three separate benzidine-based dyes have been classified as Group A carcinogens; these may be counted separately or as a group.

Question 77. Does EPA know how many agents it has classified as Group A carcinogens?

Response: It depends on how they are counted, but the EPA does know which agents it has classified as Group A carcinogens.

Question 78. Were risk assessments done on each substance classified as a Group A carcinogen?

Response: Yes.

Question 79. For each Group A carcinogen, list the relative risk associated with that carcinogen.

Response: See attached Table. Relative risk estimates are not comparable to each other for potency purposes, since relative amounts of exposure or dose differ.

Question 80. For other substances classified as carcinogens, list the relative risk for each substance.

Response: There are too many risk assessments to answer this question explicitly, but relative risk estimates from individual studies can vary from less than one to over 10.

Question 81. Will the EPA submit a list of Group A carcinogens and the documents which form the basis for each classification?

Response: See the attached table for list of Group A carcinogens. The risk assessments for these documents can be found on the enclosed CD-ROM (Attachment 6), with the exception of radon, for which the technical support document (Attachment 7) is provided.

Relative Risk

Question 82. Wouldn't you agree that the lower the relative risk the less likely that there is an association between the substance and an effect?

Response: Not necessarily. As described by Rothman (1986) when one considers the evidence for a causal association one of the nine factors considered is strength of association, which he describes as follows:

> "Strength. By "strength of association," Hill[2] means the magnitude of the ratio of incidence rates. Hill's argument is essentially that strong associations are more likely to be causal than weak associations because if they were due to confounding or some other bias, the biasing association would have to be even stronger and would therefore presumably be evident. Weak associations, on the other hand, are more likely to be explained by undetected biases. Nevertheless, the fact that an association is weak does not rule out a causal connection. It has already been pointed out that the strength of an association is not a biologically consistent feature but rather a characteristic that depends on the relative prevalence of other causes." [Emphasis added.]

For example, an average smoker's relative risk of lung cancer, which has relatively few risk factors in the typical environment, is 10-20. The same smoker's relative risk for heart disease, however, which has several other strong environmental or behavioral risk factors, is only about 1.8.

Question 83. Wouldn't you agree that once a relative risk is below a certain level it is difficult to use epidemiologic studies to predict cause and effect?

Response: Yes, but other factors apply. Relative risk is a measure of strength of association. It is one of nine criteria used to show causal association. The nine criteria suggested by Hill (1965) are as follows: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biologic gradient, (6) plausibility (7) coherence, (8) experimental evidence, and (9) analogy.

None of these nine points bring indisputable evidence for or against the cause and effect hypothesis and none can be required as sine qua non except for temporality. Therefore, even though a relative risk is found to be below a certain level, epidemiologic studies can still be used to show cause and effect.

Question 84. Wouldn't you agree that a relative risk of less than two is generally considered to be very weak?

Response: No. See responses to Questions 82 and 83.

Question 85. Of the substances classified as Group A carcinogens, how many had a relative risk of less than two?

Response: ETS, for lung cancer at typical environmental levels. The other Group A carcinogen designations are based on epidemiology studies of high occupational levels of exposure (or pharmaceutical exposures in the case of DES).

Question 86. Are there any other substances classified by EPA as a Group A carcinogen where the relative risk is 1.19 or less? What other substances classified by EPA as carcinogens where the relative risk is 1.19 or less?

Response: None of the substances classified by EPA as a Group A carcinogen have relative risk of 1.19 or less. For other classifications such as Group B (probable human carcinogen) and C (possible human carcinogen), usually either the human evidence is inadequate or human data are lacking. For these Group B and C carcinogens, animal studies have shown increased cancer incidence. There are many of these Group B and C substances in which the relative risks for some doses are less then 1.19.

Question 87. Isn't it true that in document number EPA/600/6-90/005A entitled "Evaluation of Potential Carcinogenicity of Electromagnetic Fields Prepared by the U.S. EPA Office of

Health and Environmental Assessment" that EPA concluded "[t]he Association between cancer occurrence and exposure to either EMF or RF fields is not strong enough to constitute a proven causal relationship, largely because the relative risks in the published reports have seldom exceeded 3.0 in both childhood residential exposures and in occupational situations." Does the EPA stand behind that statement?

Response: The quote from the EMF document is from a review draft document and does not represent EPA policy or conclusions, as indicated by the fact that the draft is stamped "Do Not Cite or Quote." The quote, from page 6-2 of the draft document, is not from the conclusions section but rather from the section on Epidemiology Research Needs. The context indicates that further epidemiologic research is needed on EMF. Relative risk is only one factor in determining a causal relationship.

Question 88. If a relative risk for substance "X" is 1.19, without controlling for another factor as a confounder, which other factor is later demonstrated to be a relative risk greater than 3.0 for the same disease, doesn't that later information in and of itself demonstrate the need to reevaluate the relative risk of substance "X" in light of a confounder which could overrule and explain the association.

Response: No, not in and of itself. For example, if the other factor (confounder) has a relative risk of 3.0 for the same disease as factor "X" (RR=1.19), but is present in only 1% of the population while factor "X" is present in 50% of the population, adjustment for this confounder would not materially change the relative risk for factor "X". Therefore, it is neither going to overrule nor explain the association.

Meta-Analysis

For all of these Questions (89-94), meta-analysis will be defined as the process of combining study results (similar to the wording in Question 94). While the meta-analysis techniques used in EPA reports often differ from compound to compound, the concept of combining similar type studies to derive conclusions about a compound is used in all EPA reports.

Question 89. List all the substances classified as Group A carcinogens where meta-analysis was used to prepare the risk assessment.

Response: All of the risk assessments listed in the Table in the "Group A Carcinogens" responses use meta-analysis in some form, depending on the number of available studies. Asbestos, benzene, and nickel are three examples of different types of meta-analysis for EPA Group A carcinogens.

Question 90. Name all the substances classified as carcinogens where meta-analysis was used in the risk assessment.

Response: The scope of the question is too broad for EPA to provide an itemized response. Many agencies throughout the world classify carcinogens; all have differences in their procedures for combining data. However, the National Academy of Sciences in 1986 and the National Institute of Occupational Safety and Health in 1991, performed meta-analysis on the ETS lung cancer database.

Question 91. How many times has meta-analysis been used by EPA in conducting risk assessments?

Response: There are too many EPA risk assessments to examine all the reports. The general procedure is to combine data for hazard identification purposes, but use the most sensitive study for quantitative estimation. See also the response to Question 89.

Question 92. List those substances for which meta-analysis was used.

Response: See the response to Question 91.

Question 93. Has the EPA reported all meta-analysis it has conducted on ETS?

Response: Yes.

Question 94. Isn't meta-analysis the process of combining studies? What steps must be taken in advance of such combination to ensure that they are suitable for such meta-analysis? Did the EPA follow such procedures prior to performing a meta-analysis on ETS? If so, please provide all documentation relating to EPA's application of the procedures.

Response: EPA's documentation for the selection of studies is presented in Chapter 5 (for lung cancer) and Chapter 7 (for noncancer respiratory effects) of the ETS report (Attachment 2). The documentation for "tiering" of the ETS lung cancer studies is presented in Appendix A and the documentation for the weighting of the ETS lung cancer studies is presented in Appendix D.

Benefit-Cost Analysis

Question 95. EPA's draft benefit-cost analysis assumes that the cost of the proposed restrictions will be limited almost exclusively to providing smoking lounges for a small subset of the smoking population (10 to 20 percent). Is it reasonable to assume there will not be any costs associated with the other 80 to 90 percent for whom your analysis assumes lounges will not be provided?

Response: The total costs which are estimated in the report include policy development and implementation costs for individual establishments (Exhibit 1-1, 1-2), smoking lounge costs (Exhibits 1-1 through 1-4), and costs of national enforcement (Exhibit 1-5). All of these costs are discussed in "The Costs and Benefits of Smoking Restrictions: An Assessment of the Smoke-Free Environment Act of 1993 (H.R. 3434)" (pages ES-4-5, and pp 4-8) (see Attachment 8).

Question 96. The primary burden of the proposed restrictions will fall on the million of Americans who choose to smoke. How can a benefit-cost analysis be meaningful if it completely ignores these individuals' costs?

Response: We do not believe that any relevant cost or benefit categories were ignored in this analysis. However, while all relevant costs and benefits were addressed, several were left unquantified. These unquantified issues include expected increases in productivity and improved comfort of smokers and nonsmokers from reduced ETS, anticipated improvements in health and reduced premature deaths of smokers, and expected decreases in productivity and decreased enjoyment of smokers due to restrictions on their smoking. While these issues were not quantified, they were identified and discussed in the document (pages ES-7-9, ES-10-11, ES-14 and pages 14-15, 22-23, 28-30) (see Attachment 8). Accordingly, as stated in the document, the unquantified losses would have to exceed the unquantified benefits by more than $39 billion to $72 billion per year in order for costs to exceed benefits (page ES-14 and page 32).

Question 97. EPA's draft benefit-cost analysis looks only at one option, HR 3434. Shouldn't less draconian alternatives be examined to see if most of the alleged benefits could be achieved at lower cost?

Response: EPA was asked to conduct a cost-benefit analysis of H.R. 3434. No alternative formulations of this proposed legislation were presented, and none were assessed (see Attachment 8, page ES-11 and page 30).

EPA Grants

Question 98. Could the EPA please provide a list of each and every grants (whether research, publication or other) that the EPA has issued on the subject of environmental tobacco smoke and/or indoor air quality. Please include the name and address of the recipient(s) of the grant, the amount of the grant, the effective dates of the grants, all identifying grant numbers, and please state as well, the purpose of each grant.

Response: Given the magnitude of the scope of your request, it would be extremely burdensome, time-consuming and labor intensive to gather and produce for you all the above-requested information. For example, under section 103 of the Clean Air Act alone, EPA has processed over 600 grants during the past 5 years. EPA does not maintain a separate listing of subcategories such as environmental tobacco smoke or indoor air. However, if you would like specific information about any particular grant or grants, we would be happy to provide you with such information or documentation.

Question 99. Please provide and produce all EPA documents relating to each such grant.

Response: See response to question 98.

Question 100. Please provide a list of each and every EPA grant to a scientific journal that publishes research.

Response: EPA does not provide grants to scientific journals.

Question 101. Provide a list of all grants to current or prior SAB members or their employing institutions.

Response: There are over a thousand prior SAB members and approximately 400 current members and consultants who may have received grants from EPA at one time or another. Neither EPA nor the SAB maintains records on the recipients of such grants or their employing institutions. Therefore, given the magnitude of the scope of your request, it would be extremely burdensome, time-consuming and labor-intensive to produce for you a list of all grants to such individuals or their employing institutions. However, if you would like specific information about any particular individual or individuals, or a particular grant or grants, we would be more than happy to obtain this information for you.

Responses to Questions 79 and 81

SUBSTANCES CLASSIFIED BY EPA AS GROUP A CARCINOGENS

Substance	Relative Risk Estimates*	Type of Exposure	Comments
Arsenic	2-10 times expected lung cancer mortality	occupational	There are also epidemiological studies finding an association between arsenic in drinking water and skin cancer.
Asbestos	Largest study reports: lung cancer SMR=416 and 175 mesotheliomas in 17,800 workers (none expected)	occupational	Mesothelioma is a rare tumor type.
Benzene	2-6 times expected leukemia incidence/ mortality	occupational	
Benzidine	13 of 25 workers had bladder tumors in one study	occupational	
Bis(chloromethyl)-ether[and commercial grade chloromethyl methyl ether, which contains BCME as a contaminant]	2-10 times expected incidence of lung cancer	occupational	Induces predominantly oat cell carcinoma, a rare lung tumor type.
Chromium VI	3-31 times expected lung cancer mortality	occupational	
Coke Oven Emissions	RR=2.5-3.5 for lung cancer	occupational	
Diethylstilbestrol	vaginal and cervical cancer risk = 0.14-1.4/1000 exposed in utero	pharmaceutical	
Direct Black 38 Direct Blue 6 Direct Brown 95 [Benzidine-based dyes]	RR=6.8 for bladder cancer from exposure to mixed dyes	occupational	No human data exist for exposure to any dye alone; however, these dyes contain residual benzidine and are metabolized to benzidine, a known human carcinogen.
Environmental Tobacco Smoke (ETS)	RR=1.3 for lung cancer based on combined U.S. studies (RR=1.6 with spousal smoking)	environmental	Pooled relative risk estimates calculated from U.S. epidemiological studies of spousal exposure.
2-Naphthylamine	12 of 48 workers developed bladder tumors in one study	occupational	

Substance	Relative Risk Estimates*	Type of Exposure	Comments
Nickel (Nickel Refinery Dust and Nickel Subsulfide)	lung cancer SMR=298-510 nasal cancer SMR=1583-26,667	occupational	Nickel subsulfide makes up roughly 50% of nickel refinery dusts. Nasal cancer is rare.
Radon	lung cancer RR=2-6 in underground miners	occupational	
Vinyl Chloride	liver cancer RR=2.4-16 (including angiosarcomas)	occupational	Angiosarcoma is a rare tumor type.

*Relative risk estimates are derived from epidemiology studies of occupational exposures for all substances with the exception of diethylstilbestrol (pharmaceutical exposures) and ETS (environmental exposures). Relative risk estimates are not comparable to each other for potency purposes, since relative amounts of exposure or dose differ.

REFERENCES FOR TABLE

U.S. EPA. Health Assessment Document for Inorganic Arsenic. 1984.

U.S. EPA. Airborne Asbestos Health Assessment Update. 1986.

U.S. EPA. Health Effects Assessment for Benzene. 1989.

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U.S. EPA. Carcinogen Assessment of Coke Oven Emissions. 1984.

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U.S. EPA. Health and Environmental Effects Profile for Direct Black 38. 1987.

U.S. EPA. Health and Environmental Effects Profile for Direct Blue 6. 1987.

U.S. EPA. Health and Environmental Effects Profile for Direct Brown 95. 1987.

U.S. EPA. Evaluation of the Potential Carcinogenicity of 2-Naphthylamine. 1988.

U.S. EPA. Health Assessment Document for Nickel and Nickel Compounds. 1986.

U.S. EPA. Technical Support Document for Citizen's Guide to Radon. 1992.

U.S. EPA. Health Effects Assessment for Vinyl Chloride. 1984.

Relative Risk

ATTACHMENT 1

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

EPA-SAB-IAQTHEC-91-007

April 19, 1991

OFFICE OF
THE ADMINISTRATOR

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board's review of the Office of Research and Development document Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children, EPA/600/6-90/006A, June 1990, and the Office of Air and Radiation's draft document Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies, (EPA/400/6-90/004), June 1990.

Dear Mr. Reilly:

On November 1, 1990, the Offices of Research and Development and Air and Radiation requested that the Science Advisory Board (SAB) review the above referenced draft reports. The first document (hereafter referred to as the risk assessment report) incorporates a health risk assessment of the impact of passive smoking (i.e., exposure to environmental tobacco smoke, or ETS) on adult lung cancer incidence, and a discussion of the effects of exposure to ETS on the incidence and prevalence of respiratory disorders in children. The risk assessment report was prepared at the request of the Indoor Air Division, Office of Air and Radiation, to provide information and guidance on the potential hazards of indoor air pollutants. The second document (hereafter referred to as the policy guide) reflects and parallels the risk assessment report, but was not developed as a scientific document

The Agency sought the advice of the SAB's Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) concerning the risk assessment's accuracy and completeness, and the Committee's opinion on whether the weight of available evidence supported the conclusions drawn concerning ETS's roles in causing lung cancer in adults and respiratory disease in children. The SAB was also requested to review that portion of the policy guide which presented a scientific database on ETS.

The IAQTHEC met on December 4 and 5, 1990, in Arlington, Virginia to conduct its review of the ETS draft documents. In summary, the Committee found the risk assessment document to be a good faith effort to address complex and difficult issues affecting public health. The authors attempted to select and interpret the most relevant information from an enormous and diverse scientific data base, most of which was not designed or intended to yield the information needed for this task. Since the task is extremely difficult, it should come as no surprise that the Committee also found the document to be incomplete in many respects. The situation is analogous to that for the Criteria Air Pollutants, wherein it has been necessary to prepare and review two or more draft criteria documents prior to their endorsement by the Clean Air Scientific Advisory Committee. The IAQTHEC has suggested changes both in the organization and specific technical content of the draft, that if followed, can result in an improved ETS risk assessment document. The Committee also suggested changes that would strengthen the use of the incorporated scientific database to support the recommendations contained in the policy guide.

The Charge to the Committee, and associated findings of the Committee are outlined below:

A. Carcinogenicity Issues

1. Carcinogenicity of ETS Has EPA met the requirements stated in its carcinogen guidelines for characterizing ETS in Category A, i.e., is the evidence sufficient to conclude that ETS is causally associated with lung cancer?

The Committee concurs with the judgment of EPA that environmental tobacco smoke should be classified as a Class A Carcinogen, but notes that it had some difficulty in applying the Guidelines for Carcinogen Risk Assessment (51 FR 33992), as they are currently formulated, to this complex and variable mixture. We advise EPA to place greater weight on the biological considerations and the extensive experience with active human smoking to support the classification.

2. Spousal Smoking Is spousal smoking a proper measure of ETS exposure to assess lung cancer risk?

Despite its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a feasible method for identifying people with greater, versus lesser, ETS exposure. There are potential important confounders related to spousal smoking status as a measure of exposure, but such confounding concerns are present in other surrogates of exposure as well.

3. United States and Foreign Studies Are the differences in relative risk observed between studies in the U.S. and those overseas of concern, and if so, to what degree?

The Committee believes that data from studies conducted in other countries, as well as in the United States should be utilized in evaluating whether exposure to ETS increases risk of lung cancer, and does not find the observed differences to be of concern. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted.

4. Use of Meta-Analysis Is Meta-Analysis an appropriate tool to use in the document and has it been applied correctly? Have the epidemiological studies been properly evaluated and combined using this technique?

Meta-analysis is a general term applied to a wide range of techniques intended to synthesize findings across related studies. Although it is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS, the emphasis given the meta-analysis of ETS/lung cancer association in this report is not justified. Biological considerations related to respiratory carcinogenesis and extrapolations from human exposure via active smoking provide compelling evidence that is consistent with the results of the meta-analysis.

5. Confounders/Misclassification Have the most important confounders been properly addressed? Has the issue of misclassification (classifying current and former smokers as "never smokers") been adequately addressed and the proper adjustments made? Are there other confounders which could be addressed in greater detail?

Important potential confounders of the ETS-lung cancer relationship were addressed in the report mainly, by carrying out a separate meta-analysis of those studies which included adjusted analyses. The potential main confounders included in these adjusted analyses were age and surrogates for confounding factors, including education, and social class. Comparison of relative risks in those studies which analyze both factors suggests that these effects are not important confounders. As for other potential confounders of the ETS-lung cancer relationship, including occupation, radon exposure, and diet, there is no way to evaluate their importance as confounders or to adjust for them, since virtually none of the studies contains information on them.

6. Characterization of Uncertainties Does the document characterize the uncertainties, both in the weight-of-evidence and the number of attributable deaths, appropriately?

Vis-a-vis weight of evidence, the draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high, given the known effects of active smoking and the known composition of ETS (e.g. the carcinogenicity of ETS in some animal studies, and the presence of known human carcinogens in ETS); and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer. These together appear to argue for a positive effect. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

7. Quantitative Risk Assessment Has the quantitative risk of lung cancer been properly assessed? Would it be more properly assessed by a dose response assessment using either cotinine or respirable suspended particulate matter as surrogate measures of exposure (Appendix C)? Would it be more properly assessed with alternative modeling approaches (Appendix D)? Should a dose-response model be developed for ETS-radon interaction effects?

The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis is a suitable approach to combining the data. This approach is direct and makes the fewest assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens. Given that the epidemiology studies should be the basis of the risk assessment, some suggestions for refinements of the risk assessment are detailed in our report.

8. Home vs. Workplace Exposure Should the Draft Report attempt to distinguish between the effects of home vs. workplace exposure to ETS?

The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace, and therefore on the relative impacts of home and workplace exposure. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area.

B. Respiratory Disorders in Children

1. Weight of Evidence Has the weight of evidence for ETS related respiratory disorders in children been properly characterized? A draft report with a detailed description and analysis of 26 recent studies has recently been prepared and is enclosed. It is in a form similar to that of Appendix A. Should it be included in a revised report as Appendix E?

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed. The weight of the evidence could then be judged to determine the causality of associations.

The additional literature available since 1986 provides a basis for increased concern about the effects of ETS exposure on respiratory disorders. Thus, the Committee urges a thorough review of the entire body of evidence, including earlier reports covered in the 1986 reports of the Surgeon General and National Research Council. This review could be included in the revised risk document as Appendix E.

2. **Confounders** Have confounders in the epidemiologic studies been adequately addressed?

A number of confounders were mentioned by the report, but addressed improperly, including *in utero* exposure, parental reporting bias, and active smoking. One must stress both the biological precursors important to the effects of ETS in childhood, and the socioeconomic and behavioral factors.

3. Use of Meta-Analysis Should a meta-analytic approach be attempted as in the lung cancer analysis?

The Agency should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of studies suitable for such an analysis.

C. Review of the Policy Guide

The Committee found, with some exceptions detailed in our report, that the scientific database incorporated in the policy guide is correct and appropriate. The policy guide should be revised to reflect changes made to the risk assessment report.

We appreciate the opportunity to review these issues, and stand ready to provide review comments on any significant revisions to the subject documents. We look forward to your response on the major points we have raised.

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Science Advisory Board

Morton Lippmann

Dr. Morton Lippmann, Chairman
Indoor Air Quality and Total
Human Exposure Committee

ENCLOSURE

EPA

U.S. Environmental
Protection Agency

Washington, DC
EPA-SAB-IAQTHC-91-007

REPORT OF THE INDOOR AIR QUALITY AND TOTAL HUMAN EXPOSURE COMMITTEE

REVIEW OF THE OFFICE OF RESEARCH AND DEVELOPMENT'S DRAFT REPORT "HEALTH EFFECTS OF PASSIVE SMOKING: ASSESSMENT OF LUNG CANCER IN ADULTS AND RESPIRATORY DISORDERS IN CHILDREN"

(EPA/600/6-90/006A)

A SCIENCE ADVISORY BOARD REPORT

APRIL, 1991

ABSTRACT

The Indoor Air Quality and Total Human Exposure Committee (IAQTHEC) met on December 4/5, 1990, to conduct its review of the environmental tobacco smoke (ETS) draft documents. In summary, the Committee found the risk assessment document to be a good faith effort to address complex and difficult issues affecting public health. Since the task is extremely difficult, it should come as no surprise that the Committee also found the document to be incomplete in many respects. The IAQTHEC has suggested changes both in the organization and specific technical content of the draft, that if followed, can result in an improved ETS risk assessment document. The Committee also suggested changes that would strengthen the use of the incorporated scientific database to support the recommendations contained in the policy guide.

The Charge to the Committee, and associated findings of the Committee are outlined below:

A. Lung Cancer in Adults

1. Carcinogenicity of ETS The Committee concurs with the judgment of EPA that environmental tobacco smoke should be classified as a Class A Carcinogen.

2. Spousal Smoking Despite its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a feasible method for identifying people with greater, versus lesser, ETS exposure.

3. United States and Foreign Studies The Committee believes that data from studies conducted in other countries, as well as in the United States should be utilized in evaluating whether exposure to ETS increases risk of lung cancer.

4. Use of Meta-Analysis It is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS, but the emphasis given the meta-analysis of ETS/lung cancer association in this report is not justified.

5. Confounders/Misclassification Important potential confounders of the ETS-lung cancer relationship were addressed in the report. Comparison of relative risks (RRs) in those studies which analyze relevant factors suggests that these effects are not important.

6. Characterization of Uncertainties The draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high; and (2) the accumulating epidemiologic evidence on the relationship

between exposure to ETS and lung cancer. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

7. Quantitative Risk Assessment The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis is a suitable approach to combining the data.

8. Home vs. Workplace Exposure The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area.

B. Respiratory Disorders in Children

1. Weight of Evidence In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed. The weight of the evidence could then be judged to determine the causality of associations.

2. Confounders A number of confounders were mentioned by the report, but addressed improperly, including *in utero* exposure, parental reporting bias, and active smoking.

3. Use of Meta-Analysis The Agency should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of studies suitable for such an analysis.

C. Policy Guide The Committee found, with some exceptions detailed in the report, that the scientific database incorporated in the policy guide is correct and appropriate.

KEYWORDS: Environmental Tobacco Smoke (ETS); Carcinogenicity; Passive Smoking; Sidestream Smoke; Meta-analysis; Confounders; Lung Cancer; Respiratory Disease

U. S. ENVIRONMENTAL PROTECTION AGENCY

NOTICE

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U.S. Environmental Protection Agency
Science Advisory Board
Indoor Air Quality and Total Human Exposure Committee

Environmental Tobacco Smoke Review

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1.0 EXECUTIVE SUMMARY

The Committee's review of the environmental tobacco smoke (ETS) Risk Assessment document and Policy Guide found them to be good faith efforts to address complex and difficult issues affecting public health. The authors attempted to select and interpret the most relevant information from an enormous and diverse scientific data base, much of which was not designed or intended to yield the information needed for this task. Since the task is extremely difficult, it should come as no surprise that the Committee also found the documents to be incomplete in many respects. The situation is analogous to that for the Criteria Air Pollutants, where it has been necessary to prepare and review two or more draft documents prior to their endorsement by the Clean Air Scientific Advisory Committee (CASAC). This Committee has suggested both organizational and specific technical changes and additional analyses that, if followed, should result in improved ETS Risk Assessment and Policy Guide documents. The Committee stands ready to provide further review comments on the revised drafts.

The SAB was asked to address the following issues in reviewing the documents.

A. Lung Cancer in Adults

The Committee noted that Chapters 3 and 4 draft risk document addressed only the issue of lung cancer risk for non-smoking women due to spousal smoking. It is suggested that the revised document be expanded to include the full range of cancer impacts of ETS. The Committee also noted a number of areas where considerable improvements could be made organizationally, and in terms of substantive content--particularly regarding material that was not adequately covered or not covered at all. We urge the EPA staff to redraft those chapters as well. Furthermore, we recommend the addition of a new chapter addressing addressing the physical, chemical, and dose considerations of ETS in relation to the same considerations for active smoking.

Findings on specific issues within the broader context of lung cancer in adults follow:

1. Carcinogenicity of ETS Has EPA met the requirements stated in its carcinogen guidelines for characterizing ETS in

Category A, i.e., is the evidence sufficient to conclude that ETS is causally associated with lung cancer?

The Committee concurs with the judgment of EPA that environmental tobacco smoke should be classified as a Class A Carcinogen, but notes that it had some difficulty in applying the Guidelines for Carcinogen Risk Assessment (51 FR 33992), as they are currently formulated, to this complex and variable mixture. The draft risk assessment document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high, given the known effects of active smoking and the known composition of ETS (e.g. the carcinogenicity of ETS in some animal studies, and the presence of known human carcinogens in ETS); and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer. These together appear to argue for a positive effect. We advise EPA to place greater weight on the biological considerations and the extensive experience with active human smoking to support the classification.

2. Spousal Smoking Is spousal smoking a proper measure of ETS exposure to assess lung cancer risk?

Despite its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a feasible method for identifying people with greater, versus lesser, ETS exposure. The problems in not accounting for background exposure from other sources would, if anything, bias against finding increased risk of lung cancer. Bias related to misclassification associated with smoking status has been addressed and corrected for in this draft report. There are possible confounders related to spousal smoking status, but such confounding concerns are present in other surrogates of exposure as well. The potential importance of these confounders has been determined not to be sufficient to alter the conclusion that ETS increases the risk of lung cancer.

3. United States and Foreign Studies Are the differences in relative risk observed between studies in the U.S. and 'those overseas of concern, and if so, to what degree?

The Committee believes that data from studies conducted in other countries, as well as in the United States, should be utilized in evaluating whether exposure to ETS increases risk of lung cancer. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted.

4. Use of Meta-Analysis Is Meta-Analysis an appropriate tool to use in the document and has it been applied correctly? Have the epidemiological studies been properly evaluated and combined using this technique?

Meta-analysis is a general term applied to a wide range of techniques whose objective is to synthesize findings across related studies. Although, it is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS, the emphasis given the meta-analysis in this report in attempting to demonstrate that ETS is causally associated with lung cancer is not justified. Biological considerations related to respiratory carcinogenesis (e.g., biologic plausibility) are equally compelling. Given the similarities in composition between mainstream smoke and ETS, biological considerations related to respiratory carcinogenesis and the extensive evidence on active smoking should receive greater weight.

5. Confounders/Misclassification Have the most important confounders been properly addressed? Has the issue of misclassification (classifying current and former smokers as "never smokers") been adequately addressed and the proper adjustments made? Are there other confounders which could be addressed in greater detail?

Important potential confounders of the ETS-lung cancer relationship were addressed in the report mainly by carrying out a separate meta-analysis of those studies which included adjusted analyses. The potential main confounders included in these adjusted analyses were age and surrogates for confounding factors, including education, and social class. Comparison of unadjusted and adjusted relative risks (RRs) in those studies which present both factors suggests that these effects are not important confounders.

As for other potential confounders of the ETS-lung cancer relationship, including occupation, radon exposure, and diet, there is no way to evaluate their importance as confounders or to adjust for them, since virtually none of the studies contains information on them.

The issue of misclassification should not be restricted to misclassification of current smokers and ex-smokers as "never smokers." It should also be mentioned that misclassification of diagnosis (diagnoses other than lung cancer being incorrectly classified as lung cancer; or vice versa) will cause a biasing of the RR toward the null.

Not enough attention was given to possible non-differential misclassification of ETS exposure. This is an important issue, since marriage to a smoking spouse is an imperfect proxy for total ETS exposure. In the case of dichotomous exposure, such misclassification would have the effect of biasing the RR estimate toward the null.

6. Characterization of Uncertainties Does the document characterize the uncertainties, both in the weight-of-evidence and the number of attributable deaths, appropriately?

Vis-a-vis weight of evidence, the draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon the two main arguments noted earlier: (1) the biological plausibility of such a causal association; and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer. With exposure levels that are usually quite low, it is not surprising that the association is likely to be weak although, given the size of the exposed population, societally important. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

Epidemiologic evidence on the relationship between exposure to ETS and lung cancer should be described more completely, with the deficiencies of individual studies used to weight their contributions to any conclusions that are drawn. The assumptions and uncertainties associated with each step of the risk assessment process ought to be explicitly stated.

7. **Quantitative Risk Assessment** Has the quantitative risk of lung cancer been properly assessed? Would it be more properly assessed by a dose response assessment using either cotinine or respirable suspended particulate matter as surrogate measures of exposure (Appendix C)? Would it be more properly assessed with alternative modeling approaches (Appendix D)? Should a dose-response model be developed for ETS-radon interaction effects?

The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis is a suitable approach to combining the data. This approach is direct and makes the fewest assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens and that those assessments are generally based on fewer studies.

Given that the epidemiology studies should be the basis of the risk assessment, some refinements of the risk assessment are recommended with respect to:

1. Criteria for Including Individual Studies in the Meta Analysis
2. Adjustment for Smoker Misclassification
3. Misclassification of Exposure
4. Uncertainties in the Estimate of Annual Lung Cancer Deaths Due to Passive Smoking
5. Dose-Response Estimation of Risk

8. **Home vs. Workplace Exposure** Should the Draft Report attempt to distinguish between the effects of home vs. workplace exposure to ETS?

The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace, and therefore on the relative impacts of home and workplace exposure. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area. The report should also review and comment on the data that exist on exposure to ETS in public places.

B. Respiratory Disorders in Children

Chapter 5 on respiratory disorders in children was a commendable first effort for a very difficult task. Nevertheless, we found that it could be substantially improved and that the conclusions drawn in it could be made much stronger if the chapter were revised in the manner suggested in this report.

The Committee found the evidence for respiratory health effects in children to be stronger and more persuasive than that stated in Chapter 5 of the draft ETS Risk Assessment document, and recommends that the new draft contain a more comprehensive discussion on quantitative risk assessment for these effects.

Specific issues are addressed below:

1. **Weight of Evidence** Has the weight of evidence for ETS related respiratory disorders in children been properly characterized? A draft report with a detailed description and analysis of 26 recent studies has recently been prepared and is enclosed. It is in a form similar to that of Appendix A. Should it be included in a revised report as Appendix E?

The additional literature available since 1986 provides a basis for increased concern about the effects of ETS exposure on respiratory disorders. Thus, the Committee urges a thorough review of the entire body of evidence, including earlier reports covered in the 1986 reports of the Surgeon General and National Research Council, and its incoporation as Appendix E.

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed. The weight of the evidence could then be judged to determine the causality of associations.

2. **Confounders** Have confounders in the epidemiologic studies been adequately addressed?

A number of confounders were mentioned by the report, but addressed improperly. These include in utero exposure, parental reporting bias, and active smoking. One must also stress both the biological precursors important to the effects of ETS in childhood, and socio-economic and behavioral factors.

3. **Use of Meta-Analysis** Should a meta-analytic approach be attempted as in the lung cancer analysis?

The Agency should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of studies suitable for such an analysis. If one is warranted, it should be guided, to the extent possible, by the same considerations outlined for meta-analysis for lung cancer.

The Committee was also asked to examine whether the draft Policy Guide's statements on health contained within the first 20 pages were scientifically defensible. With some exceptions, detailed in the this report (section 4.0), the scientific data and interpretations contained in the draft Policy Guide were appropriate. The Policy Guide draft will need to be revised to reflect the changes being made in the Risk Assessment.

2.0 INTRODUCTION

2.1 **Background** On November 1, 1990, the Offices of Research and Development and Air and Radiation requested that the Science Advisory Board (SAB) review the draft report "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," which incorporated a health risk assessment of the impact of passive smoking on lung cancer incidence. The document was prepared by the Human Health Assessment Group, Office of Research and Development, at the request of the Indoor Air Division, Office of Air and Radiation, under the authority of Title IV of Superfund (The Radon Gas and Indoor Air Quality Research Act of 1986) to provide information and guidance on the potential hazards of indoor air pollutants.

The draft risk report reviews and analyzes the data on the respiratory effects of environmental tobacco smoke (ETS) with heavy emphasis on the epidemiologic data and statistical (meta) analysis. One major portion of the Report (Chapters 3 and 4) examines the weight of evidence for lung cancer in adults. It concludes that under EPA's carcinogen assessment guidelines, ETS should be classified as a Category A or known human carcinogen.

It also estimates from epidemiology (not modeling) data that, on average, 3,800 lung cancer deaths per year in U.S. nonsmokers are attributable to ETS. The final chapter of the report examines the epidemiological evidence for non-cancer respiratory disorders in children and concludes that the detrimental respiratory effects described are associated with exposure to ETS, but that a causal association has not been established.

The draft report also contains four appendices. Appendix A provides a detailed summary and analysis of eleven recent case-control studies of ETS and lung cancer. Appendix B presents pertinent mathematical formulae and relationships. Appendix C describes the dosimetry of ETS, and Appendix D presents a potential framework for dose-response modeling for ETS and lung cancer.

The draft risk report was made available for public review and comment on June 25, 1990, with a 90-day comment period which closed Oct. 1, 1990. Over 3,500 copies were distributed and 107 public comments were received as of Oct 10, 1990. A summary of those comments were prepared and provided to the SAB Committee.

2.2 Scope of Issues/Charge to the Committee The Agency sought the advice of the SAB on the draft risk document's accuracy and completeness. The Agency also wanted an opinion on whether the weight of available evidence supported the conclusions drawn concerning ETS's role in causing lung cancer and respiratory disease. In addition, the SAB was asked to address the following specific issues:

A. Lung Cancer in Adults

1. Has EPA met the requirements stated in its carcinogen guidelines for characterizing ETS in Category A, i.e. is the evidence sufficient to conclude that ETS is causally associated with lung cancer?

2. Is spousal smoking a proper measure of ETS exposure to assess lung cancer risk?

3. Are the differences in relative risk observed between studies in the U.S. and those overseas of concern, and if so, to what degree?

4. Is meta-analysis an appropriate tool to use in the document and has it been applied correctly? Have the epidemiological studies been properly evaluated and combined using this technique?

5. Have the most important confounders been properly addressed? Has the issue of misclassification (classifying current and former smokers as never smokers) been adequately addressed and the proper adjustments made? Are there other confounders which could be addressed in greater detail?

6. Does the document characterize the uncertainties, both in the weight-of-evidence and the number of attributable deaths, appropriately?

7. Has the quantitative risk of lung cancer been properly assessed? Would it be more properly assessed by a dose response assessment using either cotinine or respirable suspended particulates as surrogate measures of exposure (Appendix C)? Would it be more properly assessed with alternative modeling approaches (Appendix D)? Should a dose-response model be developed for ETS-radon interaction effects?

8. Should the Draft Report attempt to distinguish between the effects of home vs. workplace exposure to ETS?

B. Respiratory Disorders in Children

1. Has the weight of evidence for ETS related respiratory disorders in children been properly characterized? A draft report with a detailed description and analysis of 26 recent studies has recently been prepared and is enclosed. It is in a form similar to that of Appendix A. Should it be included in a revised report as Appendix E?

2. Have confounders in the epidemiologic studies been adequately addressed?

3. Should a meta-analysis approach be attempted as in the lung cancer analysis?

The SAB was also asked to comment on the scientific foundations of a second draft document, "Environmental Tobacco Smoke: A Guide to Workplace Smoking Policies," (hereafter refered to as the "Policy Guide") produced by the Indoor Air Division of the Office of Air and Radiation.

2.3 **Conduct of The Review** The review was assigned to the SAB's Indoor Air Quality and Total Human Exposure Committee. The Committee met on December 4 and 5, 1990 in Arlington, Virginia to receive briefings from EPA staff, hear extensive comments from members of the public, and discuss the several issues embodied in the charge. Following the discussions, the Chair requested that designated Members of the Committee provide written materials organized to respond to the charge, and reflecting the preceding interactions. Those materials, after editing and review by all Members of the Committee constitute this report.

3.0 REVIEW OF THE RISK ASSESSMENT DOCUMENT

The preparation of a risk assessment document for ETS represents a formidable challenge, and the Committee recognizes the quite considerable efforts put forth by EPA staff in preparing the draft. The document contains some excellent summary materials on a large and diverse set of relevant literature, as well as some skillful and pertinent analyses that serve to address the critical issues related to the public health impact of exposures to ETS. Although we commend EPA for its efforts, we find that the document could be substantially improved, and recommend a series of specific changes in organization and content that, if followed, would make the revised document a much stronger basis for policy guidance on ETS exposure and its health effects. Since the impact of ETS on public health is comparable to that of some of the criteria air pollutants, we recommend that the revised document follow more closely the format of the Air Quality Criteria Documents. It should include additional chapters addressing the physics and chemistry of ETS, its relation to mainstream smoke, the exposures of various populations of interest to ETS, and as appropriate to the discussions of biological plausibility and weight of evidence, those aspects of dosimetry which will be needed to support other parts of the document. The contents of these additional chapters should strengthen the basis for any actions or recommendations.

The Committee also reviewed the utility, format and adequacy of the five appendices to the ETS Risk Assessment Document. We found them to be of varying utility and quality, and made specific suggestions for revisions and deletions.

3.1 **Chapter 3--Epidemiologic Evidence of Lung Cancer from ETS** The focus of this chapter is on hazard identification: that is, determining if the available evidence on ETS warrants the conclusion that exposure to ETS increases the incidence of lung cancer. As described in the Agency's "Guidelines for Carcinogen Risk Assessment," hazard identification is a qualitative process that involves review "...of the relevant biological and chemical information bearing on whether or not an agent may pose a carcinogenic hazard." The scope of hazard identification is broad, involving review of information on 1) physical-chemical properties and routes and patterns of exposure; 2) structure-activity relationships; 3) metabolic and pharmacokinetic properties; 4) toxicologic effects; 5) short-term tests; 6) long-term animal studies; and 7) human studies.

The present chapter, comprising the hazard identification step of the risk assessment, seems limited in scope when measured against the encompassing process set out by the Agency. Although the appendixes do address exposure and toxicology to an extent, this material needs more direct discussion in the chapter. The components of ETS possibly relevant to this risk assessment should be reviewed along with the characteristics of mainstream and sidestream smoke, and similarities in composition and from in vitro bioassay should be discussed. The complexity of ETS merits emphasis; it is not a single chemical agent, but a mixture with varying characteristics by place and time in relation to its formation in the burning cigarette. The toxicologic effects of individual components merit further discussion. Exhaustive review is not needed, since the Surgeon General's Reports provide comprehensive documentation.

In reviewing the human evidence, the chapter fails to draw on the voluminous evidence on active smoking and lung cancer. The 1986 Surgeon General's Report, for example, concluded that there was enough toxicologic similarity between mainstream smoke and ETS to justify using the evidence from active smoking in reaching conclusions concerning ETS and lung cancer. The evidence on active smoking and lung cancer documents the consequences of a higher level of exposure to a mixture, mainstream smoke, that resembles ETS in composition. The epidemiologic evidence on ETS and lung cancer in nonsmokers should be considered as addressing the risks of lower levels of exposure. Thus, the evidence on active smoking and lung cancer needs to be reviewed in this chapter. The causal nature of the association between active smoking and lung cancer should be described, as should exposure-response relations for active smoking and lung cancer. The Surgeon General's Reports could serve as the basis for developing this material.

The existing chapter reviews case-control and cohort studies providing information on the association of ETS with lung cancer. Characteristics of these studies are considered. Several statistical approaches are used to assess the aggregate significance of the evidence and a pooled relative risk estimate with associated confidence limits is calculated. The chapter concludes with a review of potential biases affecting interpretation of these studies, with an emphasis on misclassification.

The roster of studies selected represents those available through the time at which this draft report was released; in revising the draft, consideration should be given to substituting the data from the recent report by Janerich et al. (1990) for the earlier analysis of these same data (Varela, 1987). The features of the individual studies are adequately reviewed.

The discussion of bias (Section 3.5) needs expansion and some consideration of types of bias other than misclassification. The types of bias potentially affecting any epidemiological study include selection bias, information bias (which includes both differential and non-differential misclassification), and confounding bias. Selection bias, particularly likely to affect case-control studies based on cases and controls derived from specific institutions, should be addressed. The possibility of confounding bias merits review because of evidence that smokers are increasingly distinct from nonsmokers in socioeconomic characteristics that may have implications for health. Thus, those more highly exposed to ETS may differ from those less exposed in other relevant characteristics. Confounding, however, is an unsatisfactory explanation for the general pattern of the reported studies, with the majority showing increased risk. These studies have been conducted in a wide variety of locales with consistent findings of positive association; this consistency weighs against confounding as an explanation for the increased risk associated with marriage to a smoker. The discussion of misclassification should be expanded to include studies that have addressed the quality of information on passive smoking derived from questionnaires as well as the relation between questionnaire-based measures of exposure and biological markers of exposure. The 1990 Report of the Surgeon General includes reviews of the quality of information on smoking from surrogate respondents as well as of the validity of self-report of smoking history; this recent report should be considered and cited in the discussion of misclassification.

Two major cohort studies providing evidence on passive smoking and lung cancer have been published; a lengthy discussion is provided concerning the comparative findings of the two studies. Unfortunately, we lack information on the comparative exposures to ETS of subjects in the two populations. For both studies, followup periods began well before present methods for atmospheric monitoring or for assessing biological markers were available. Thus, arguments concerning the possibility that passive smoking is more "direct" in Japan are speculative and the lack of data should be cited and uncertainty added in drawing any conclusion concerning the comparative levels of exposure in the U.S. and Japan. The discussion of the two studies should be markedly shortened.

In summary, Chapter 3 of the May 1990 External Review Draft provides a generally adequate review and assessment of the epidemiologic evidence on ETS and lung cancer in never smokers. A complete hazard identification is not conducted, however. The chapter needs to be expanded to address more fully the toxicology of ETS and the evidence on active smoking and lung cancer. This expanded review, coupling more closely the evidence on biological plausibility that ETS is a carcinogen with the supporting epidemiological evidence would adequately support the conclusion that ETS is a Group A carcinogen, a determination that should be moved from the quantitative risk assessment (current Chapter 4) to Chapter 3. The Committee accepts this overall conclusion, in spite of the limitations of the current chapter; a more comprehensive review as suggested by the Committee should strengthen the determination that ETS is a Group A carcinogen.

3.2 Chapter 4--Assessment of Lung Cancer Risk from ETS In reviewing published quantitative risk assessments, Chapter 4 of the review draft properly dichotomizes the approaches that have been taken -- the cigarette-equivalent approach, and analyses of epidemiologic studies in which the excess lung cancer risk in nonsmokers is observed as a function of exposure to ETS. As indicated in Chapter 4, there are serious difficulties in both of these approaches. The cigarette-equivalent approach has the great advantage that it is based on relatively abundant and consistent relative risk (RR) determinations in active smokers, which can be used to project the risk in non-smokers exposed to ETS in the form of a percentage of the risk in active smokers.

The assessment of the cigarette-equivalent in non-smokers due to exposure to ETS has a considerable level of uncertainty embedded in it. The ratio of sidestream (SS) to mainstream (MS) emissions is highly variable among the components of cigarette smoke, so that the number of cigarette-equivalents to which a passive smoker is exposed varies greatly with the compound used as a marker or exposure surrogate. Neither cotinine concentration in body fluids nor the measurement of tobacco smoke particulate matter can be used with great confidence for quantitative assessment of the carcinogenic potential of ETS. There is a suggestion that the uncertainty in exposure assessment for either approach is about an order of magnitude (It should be noted here that the Guideline for Carcinogenic Risk Assessment anticipates that numerical risk estimates will have no more than one significant digit). Neither cotinine nor smoke particulate matter levels are direct indicators of carcinogenic components.

The other type of assessment is based on inferences from the epidemiologic studies of the association of exposure to ETS and carcinogenic risk in non-smokers. Since spousal smoking is a very important exposure proxy used in many studies, the utility of a categorical classification (married to a smoker/not married to a smoker) for quantitative exposure assessments needs to considered. Physical proximity of smokers to non-smokers), daily length of exposure, and exposure outside the home to ETS may be quite different in different cultures and over decades of time. Misreporting of smoking status for cases and controls in these studies may also introduce a bias. Various attempts have been made to apply corrections for these sources of bias. These attempts require further assumptions and are based on limited data available on misreporting rates and cotinine concentrations in various groups.

The assessment presented in the last section in Chapter 4 of the Review Draft does not appear to be in conflict with procedures established in other reviews, and states all assumptions made in the quantitative assessment with considerable care. The results are given in too many significant figures however.

3.3 **Chapter 5--Environmental Tobacco Smoke and Respiratory Disorders in Children** The Committee recommends that this chapter be re-organized to reflect directly the biological effects of Passive/Involuntary smoking (This terminology reverts to the original discussion of exposure-response and its impact, as per the Surgeon General reports of 1982-1986). The chapter should treat in utero exposure as a precursor to extra uterine/post birth/childhood effects, and not as a confounder. It should also be extended to address effects in adults, since the sequelae of effects in children, as well as direct effects in adults, naturally proceed from the discussion of effects in children.

The Committee's recommendations as to the structure for a revised chapter follow. In outline, the proposed sections would be: an Introduction; 1) Biological Mechanisms; 2) Exposure and its Assessment; 3) Annoyance and Irritation; 4) Acute Illnesses (middle ear, upper respiratory, lower respiratory); 5) Chronic Respiratory Systems and exacerbations of chronic obstructive pulmonary disease (COPD); 6) Asthma; 7) Pulmonary Function; and 8) Health Hazard Assessment.

The Introduction of the Chapter should include some reference to the overall problem of acute and chronic respiratory diseases, and the potential attributable risk of ETS/passive smoking (Chronic respiratory disease is the fifth leading cause of death, with an age-adjusted death rate of $15.7/10^5$ in 1985; it is increasing still. Acute lower respiratory disease is the sixth leading cause of death, with an age-adjusted death rate of $13.4/10^5$ in 1985. The prevalence rates of related conditions are significant--the rate for asthma, for example, is $4.1/10^2$ (NCHS, 1986). Acute respiratory disease is the leading cause of morbidity and disability in the U. S. (as per NCHS)).

The first section of the Chapter could be called Biological Mechanisms (5.1). It should discuss the biological plausibility of the respiratory responses (akin to the discussion of carcinogenicity), and a brief discussion of the comparable response to active smoking. Such topics as irritant responses to pollutants (as are found in ETS) have been discussed at length in EPA Office of Research and Development and Office of Air Quality Planning and Standards (OAQPS) documents (e.g., National Ambient Air Quality Standards (NAAQS) Criteria Documents and Staff Papers, and National Emissions Standards for Hazardous Air Pollutants (NESHAP) Criteria Documents.

It should start with the effects of *in utero* exposure effects as precursors to childhood effects (5.1.2.): reduced fetal oxygenation, poorer lung (and brain) development, low birth weight, immunological and biochemical effects (e.g., changes in T cells and immunoglobulin levels, changes in prostaglandin regulation, protease inhibitors) (Amer. Acad. Peds. J. Peds., 1976; ALK report, 1983; Wall et al., 1985; Rantakallio, 1978; McIntosh, 1984; Tager, 1988).

The next discussion (5.1.3) could be of the effects of low lung function at birth (due to genetics and in utero exposure) as a precursor of lower respiratory infections; poorer lung development (disposing to greater effects of ETS on lung growths) (Martinez et al., 1989; Sherrill et al., 1990; Lebowitz, 1991), as discussed at the Committee's meeting).

There should be a discussion (5.1.4) of the potential reduction in host defense mechanisms due to ETS (going further than that induced by in utero passive smoking), which is of a similar nature (though a different dose) to that induced by active smoking. This topic relates to the increased predisposition to and prevalence rates of acute illnesses (middle ear, upper respiratory, lower respiratory, other exacerbations of chronic respiratory disease/chronic obstructive pulmonary disorder/airway obstructive disease (COPD/AOD)).

The next logical discussion (Section 5.1.5) could concern how these experiences could lead to chronic respiratory disease (e.g., chronic cough, persistent wheeze) in childhood, and how the sequelae of such would be chronic respiratory disease in adult life. The pathophysiological and anatomical mechanisms would be featured, and some discussion of biochemical mediators would occur.

There should be a discussion (5.1.6) of the biological reasons why ETS would produce or exacerbate bronchial lability and responsiveness (BR) (coupled to the lower airway caliber, and possibly genetics, discussed above), and how this BR, especially in conjunction with increased Immunoglobulin E and lower respiratory infections (both discussed above) could lead to childhood wheezy bronchitis and asthma (Tager, ARRD, '88; 138:507; Burrows and Martinez, ARRD, '89 140:1515). The role of atopy (also genetically regulated) in this process should be discussed (ibid.).

The role of these above-mentioned conditions (BR, bronchitis, asthma/persistent wheeze) on decreased lung growth (Sherrill, op cit.) should be discussed. This could lead into a general discussion (5.1.7.) of why lower lung function is related pathophysiologically to ETS, starting with deceased lung growth in utero (see above), and how this would lead to low lung function/COPD in adults (Tager et al., 1987; Lebowitz et al., 1987). Appropriate biochemical and anatomic mechanisms would be discussed.

Unless the relevant material is covered generically in an earlier chapter, Exposure and its Assessment could be covered in a seperate second section (5.2). Such a section would cover reported exposures, measurements of indoor nicotine, other related pollutants (PM, CO, etc.), and biological markers such as cotinine (Jarvis et al., 1987). Factors associated with ETS (cf., Sandler et al., 1989) should be presented as relevant. Other methods of exposure estimation and assessment should also be discussed, including utilization of models based on source characterization from chamber studies. The relationships between reported exposures and monitoring results, and biases in reporting (cf., Friedman et al., 1983) could be discussed also. Confounding needs to be discussed (Quackenboss et al., 1989; Lebowitz, 1990) as well (other key references include National Research Council (NRC) 1981; World Health Organization (WHO) 1982; NRC 1986, and WHO/EURO Proceedings on Indoor Air 1984, 1987, and 1990.) Further, exposure-dose estimation would be presented (Hiller et al., 1982).

The third section (5.3) should address Annoyance and Irritation. Annoyance is important per se, and annoyance also affects subjective reports (Lebowitz, 1989; Department of Health, Education, and Welfare 1971; National Institute of Occupational Safety and Health 1971; National Clearinghouse on Smoking and Health 1976; NRC 1981, Surgeon General's Report 1986) (Odor topics should be included in this section, introducing the concept of sensitive individuals). Irritation effects are well-documented (Weber, and Hugod, 1984), and occur more quickly at lower doses in those more "sensitive" (ibid., op cit). Acute irritant symptoms should be a major topic. This section should document such effects in children and adults, and differentiate irritant from infectious and allergenic effects.

The fourth section (5.4) should cover Acute Illnesses. This includes middle ear effusions (5.4.1), upper and lower respiratory illnesses (including such exacerbations of COPD) (5.4.2-.4), and sequelae of lower respiratory illnesses. The effects of LRI's on lung function (e.g., Yarnell and St. Leger 1979), and the possibility of LRI's leading to asthma in children (Gregg, 1973) warrants discussion. The effects of LRIs leading to asthma in children (Gregg, 1973) should also be discussed. The effects of LRIs also includes AOD in adults (the overall effects of childhood respiratory troubles (CRT)), especially as documented in longitudinal studies (Lebowitz et al. 1987, 1988; and Sherrill et al. 1990); this could be a separate section (5.4.6).

Airway obstructive disease should be addressed in a major section because of the well-documented effects of ETS on lower respiratory tract illnesses, and the above-mentioned sequelae. The EPA report did a reasonable job in this area, and can be expanded (by incorporating some of the comments included in the reviews by Samet and Lebowitz). Further discussion of biases in reporting are available (Colley 1974; Cederlof and Colley 1974), as well as for confounding by other exposures (Hammer et al. 1976; Anderson, 1979; Speizer et al. 1980; Comstock et al., 1981; Melia et al. 1982; Koo et al. 1988), and interactions with other exposures (Lebowitz et al. 1989 and 1990). There should also be discussion of the concurrent effects of breast feeding and socio-economic status (Martinez et al., '89, '90).

The fifth section should cover Chronic Respiratory Symptoms (and increases of symptomatology in COPD as exacerbations). Some of this topic was covered in the EPA report, but it could be improved by clarification and expansion (see reviews provided). Again, biases in reporting, confounding by other exposures, and interactions of exposures producing responses (ibid., op cit.) warrant discussion. Effects of active/self-smoking interacting with passive smoking should be discussed (Blánd et al., 1978; Lebowitz et al. 1987 and 1988). Effects of family history (ibid., Schilling et al. 1977; Weiss et al. 1980) should also be covered. Sequelae (op cit.) could be discussed as well, and direct effects in adults also (Comstock et al. and Schilling et al., ibid.; Lebowitz and Burrows, 1976; Schwartz and Zeger, 1990).

The sixth section (5.6) should cover all the aspects of Asthma. This section is one of the most important, and was one that was insufficiently discussed (in all aspects) in the EPA report. It needs to discuss genetic and *in utero* aspects, the evidence for bronchial responsiveness, high IgE and atopy related to ETS (Weiss et al. 1983 and 1988; Tager 1988; Burrows & Martinez 1989; and Lebowitz et al. 1989 and 1990, op cit.). The effects of social status, breast feeding, other exposures, and sequelae should be discussed as well (op cit.; Rantakallio 1979; Sherman et al., 1990). Other studies, in press, could also be used (e.g., Martinez et al., Peds.). Exacerbations can be studied as well, including those seen in field studies (Quackenboss et al. and Lebowitz et al. 1989-1991, op cit.) and chamber studies (Shephard et al. 1979; Dahms et al. 1981; Stankus et al. 1988; Danuzer et al. 1991).

The seventh section (5.7) should cover effects on Pulmonary Function alluded to above, in the EPA report, including all the previous effects (and confounders, etc.) discussed above. It should be more precise, and include amount of change found.

There could be a section at this point covering other, miscellaneous topics, as in the previous report. Alternatively, these topics could be put into other sections.

The eighth section (5.8) would be a Health Hazard Assessment, which would include attributable risk and population impact. Further discussion is needed concerning the initial aspects of the section.

3.4 **Appendix A--Summary Descriptions of Eleven Case-Control Studies** The Committee agreed that Appendix A made a valuable contribution to the document, and that it should be included in the final draft. Much of the information contained in the appendix might be more useful however, if it was organized as a series of tables rather than a running text description. For example, a table that described the important characteristics of the study, e.g., population size, number of lung cancers, measure of ETS exposure used, characteristics of the control population and criteria for selecting the cases. Other tables might include potential biases addressed or not addressed in each of the studies and smoking characteristics in the background and control populations.

3.5 **Appendix B--Mathematical Formulas and Relationships** The Committee agreed that Appendix B is important to the overall report. However, in its present form, it contains several errors, both typographical and substantive, which should be corrected. Moreover, its format is difficult to read, and it is incomplete. The Committee recommends that Appendix B be restructured and rewritten in a more "reader friendly" style to include, as a minimum, the following three sections:

1. An Introduction to describe the purpose of the Appendix and its objectives.

2. An overview of the Mantel-Haenszel procedure that was used in this report for the meta-analysis. This section should also include a rationale for the selection of this proceedure, rather than the method used in the previous NRC report. Appendix B in the NRC report is suggested as a guide for the presentation of this material.

3. Description and derivations of the risk assessment equations used. A rationale for the specific equations, a discussion of the validity of these equations for case-control as well as cohort studies, and explicit assumptions pertaining to the equations should be included in this section. The Committee also suggests that the derivations be presented in a systematic format for ease of reader understanding:

    a. A new section on the derivation of the unadjusted relative risk equation. (This could be incorporated with item 2, above).

    b. A revised section on the derivation of the relative risk equation adjusted for misclassification (B1).

    c. A revised section on the derivation of the relative risk equation adjusted for background exposure (B2).

    d. A revised section on the derivation of the equation to estimate the population-attributable risk (B3).

Specific written comments pertaining to Appendix B were submitted by several Committee members. These comments identified several errors, typographical and substantial, in the equations. The Committee therefore recommends that these errors be corrected and that the results based on these equations be carefully reviewed before final publication. For example, it was acknowledged at the Committee meeting in December that the correction of one such error resulted in a slight downward shift of the predicted annual lung cancer deaths due to passive smoking.

3.6 **Appendix C--Dosimetry of ETS** The Committee agreed with EPA staff that Appendix C should be deleted in its present form. Some of the issues that are addressed in Appendix C should be addressed in at least one or more of the new chapters, but in a format appropriate to a chapter, rather than a format considered appropriate to an appendix.

When incorporating the discussion now located in Appendix C into appropriate text chapters, it should be noted that the Appendix, as written, has serious technical errors and limitations. It is seriously deficient in that it focusses entirely on carcinogens and their dosimetry in healthy adults. This is inadequate even when the endpoint of concern is lung cancer, as evidenced in the recent report of Janerich et al. (op. cit.) on the association between lung cancer in adults and their childhood exposure to ETS. It is even more inadequate in that it ignores the respiratory disorders in children that are reviewed in great detail in Chapter Five.

The whole section C-5, "INTERNAL ORGAN BURDENS FOR THE LUNG," is based upon a simplistic set of models and assumptions that produce regional lung retention times and dose estimates that are truly fanciful. It correctly states "that removal from the tracheo-bronchial region generally may be characterized by two phases. The first is a rapidly cleared phase, dominated by particles deposited on the mucus of the upper passageways. The second is dominated by particles deposited on the slowly moving mucus of distal passageways." However, the calculated half-times (C_1 and C_2) of 450 and 710 minutes, respectively, for the fast and slow phases of ETS particle clearance, differ considerably from the actual radio-aerosol study data on which the model is supposedly based, and which show much faster rates.

The literature on the effect of active smoking on particle deposition and clearance rates is misinterpreted. One study of Albert et al. (1975) concerning the short-term effects of smoking on overall tracheobronchial clearance in humans, and one study by Wanner et al. (1973) on the effects of chronic smoke exposure on mucociliary transport velocity in the trachea of the dog are cited as a basis for doubling the retention times of particles on the tracheobronchial tree as a whole. The conclusion was drawn that smoking has no effect on the regional deposition of particles. The reality is quite different. Smokers have much greater tracheobronchial deposition than nonsmokers, and the short-term effect of smoking is to greatly accelerate the clearance of particles deposited on the tracheobronchial tree. It is curious to note that the C_2 value calculated for the second "fast-phase" component in smokers is 1400 min (23.3 hours), while a 17 hour half-time was used for the "slower" alveolar region half-time in the dose calculations.

3.7 **Appendix D--Alternative Approaches for Estimating the Yearly Number of Lung Cancer Deaths in Non-Smokers Due to ETS Based on Dose-Response Modeling** The major purpose of Appendix D is to bolster the risk assessment document. Much of the data referenced in this appendix provide further evidence of the carcinogenicity of environmental tobacco smoke, and should be clearly presented in this light. For instance, the Grimmer study clearly demonstrates the lung carcinogenicity of ETS in animals. Other sections are currently incomplete and point to future directions for research. While interesting, these sections are not as supportive of the main document and may be distracting.

The first two approaches for deriving ETS dose-response models, the relative potency approach and the cigarette equivalent approach, share an implicit assumption that particle phase compounds, and polynuclear aromatic hydrocarbons in particular, are the carcinogens of interest. Other carcinogens have been identified in ETS, and many of these are in the vapor phase, e.g., benzene, vinyl chloride, formaldehyde, and several N-nitrosamines. To the degree that vapor phase carcinogens have been ignored, or incompletely collected or extracted for administration in animal experiments, the potency of ETS has been underestimated. Furthermore, the use of benzo-[a]-pyrene as a reference standard of human lung cancer is highly problematic and should be reconsidered.

The uncertainties in the relative potency approach are too great to support the derivation of an ETS dose-response model that would be an improvement over any that can be calculated from epidemiologic data. The relative potency in animals is not necessarily the same as the relative potency in humans, especially to the degree that metabolism may be involved. Furthermore, the data do not exist to support calculating the relative potency by a straightforward comparison, e.g., ETS and compound X in animal system A, compared with a known dose-response relationship for compound X in humans, so other intermediate comparisons are required, such as compound X and mixture Y with different routes of exposure, on different animals, and with different tumors. The uncertainties of each step quickly overwhelm the uncertainties in the epidemiologic studies.

The complexities of tobacco emissions complicate the cigarette equivalent approach. The referent mainstream emissions should be those of unfiltered cigarettes, upon which most of the active smoking epidemiologic data is based. The variable ratios in sidestream to mainstream emissions of toxins lead to differences in the calculated cigarette equivalents to which a passive smoker is exposed, and these may range over two orders of magnitude (see Hammond, 1990). These different emission ratios are a source of variability in the ratio of biomarkers in smokers and nonsmokers. (Metabolism rates are another potential difference.) Thus, cotinine in nonsmokers is typically less than 1% the level found in smokers, while the median level of 4-aminobiphenyl hemoglobin adducts in nonsmokers was 14% the median in smokers (Hammond et al, 1990). This corresponds to the emission ratios of these compounds, which differ by a factor of 15. Russell and coworkers (1986) (page 4-19) based their estimates of the risk of premature death from passive smoking on the ratio of cotinine in passive smokers to that in active smokers, 0.007, and assumed the same ratio held between premature deaths in passive and active smokers. The use of 4-aminobiphenyl hemoglobin adducts instead of cotinine to estimate relative exposures would have led to a higher predicted premature death rate due to passive smoking.

Several studies have been conducted on the deposition of MS and SS particles in the human lung. These should be discussed rather than relying solely on biomarkers, where the exposures are not known. A few caveats are required regarding the use of DNA adducts to estimate dose. DNA adducts are subject to repair mechanisms, and the rate of repair may differ in smokers and nonsmokers. Since nonsmokers have very different exposures to ETS, one expects a wide range in the ratio of adducts in smokers and nonsmokers. A disadvantage in the exclusive use of DNA and protein adducts as biomarkers of dose is that such markers are available for only a few suspected agents. The use of benzo[a]pyrene (BaP) DNA adducts is further complicated by the many other sources of BaP, including diet and various combustion products.

Determination of the dose-response effect of ETS based on the epidemiologic studies of Hirayama would be most valuable. The data gathered by Hirayama and colleagues could have been greatly enhanced and more generalizable if measurements of ETS levels (especially respirable particle and nicotine concentrations) had been taken in Japanese homes with varying amounts of smoking.

Some of the methods used in Appendix D might be useful in estimating the importance of ETS in respiratory diseases in children. Appendix D has information which is supportive of the main document. Some of this information can be improved; some is suggestive of future research directions. The release of the final document should not be delayed for these data. Finally, the data may be best incorporated into the relevant sections of the main document, rather than exist as an independent appendix.

3.8 Appendix E--Summary Descriptions of Twenty-Six Studies on Environmental Tobacco Smoke and Respiratory Disorders in Children

The Committee concluded that an Appendix E, similar to the Appendix A, should be included in the revised document. As before, the Committee recommends that the information by organized as a series of tables rather than as a running text description with a similar format.

4.0 REVIEW OF THE POLICY GUIDE

The Policy Guide was not prepared as a scientific document, but its recommendations are based upon summary statements of scientific knowledge. On this basis the Committee was asked to examine whether the Guide's statements on health contained within the first 20 pages were scientifically defensible. The Committee did note that there is much technical content in other sections of the Policy Guide, including technical statements on ventilation, room and building ventilation.

For the most part, the scientific data and interpretations contained in the draft Policy Guide were appropriate, but there were some notable exceptions -- an incorrect definition as to what constitutes a small particle, an erroneous statement as to the depth of penetration of mainstream smoke vs. sidestream smoke, and a misstatement of the current particulate matter NAAQS, to cite a few. Furthermore, there were statements about cardiovascular mortality, cancers at other sites, and aggravation of cardiovascular and respiratory disease that were not addressed in the ETS Risk Assessment. Thus, without having any supporting documentation, the Committee could not endorse these statements.

The Policy Guide draft will need to be revised to reflect the changes being made in the Risk Assessment. If the Committee is to review the Policy Guide again, it should be sent to the Committee with a supporting document that explicitly states the technical basis for each of its summary statements on the state of scientific knowledge.

5.0 SPECIFIC REVIEW ISSUES

5.1 Lung Cancer in Adults The Committee noted that Chapters 3 and 4 addressed the issue of lung cancer risk due to spousal smoking only for non-smoking women. It is suggested that the revised document be expanded to include the full range of cancer impacts of ETS. The Committee also noted a number of areas where substantial improvements could be made in the organization of the document, as well as in its content -- some material was not adequately covered or not addressed at all. The Committee urges the EPA to redraft those chapters as well. Some specific suggestions follow.

5.1.1 Carcinogenicity of ETS The Indoor Air Quality and Total Human Exposure Committee concurs with the finding of the draft report that Environmental Tobacco Smoke (ETS) should be classified as a Class A Carcinogen. The Committee believes, however, that the case could be made more persuasively than does the current draft document. Part of the difficulty may be found in the language and the rationale of the Guidelines for Carcinogen Risk Assessment as they are currently formulated (51 FR 33992, August 22, 1986). The Guidelines address the case of a single chemical compound which may contain contaminants or impurities. The process envisioned in the Guidelines consists of Hazard Identification and "..should include a review....to the extent that it is available" of:

1. Physical-Chemical Properties and Routes and Patterns of Exposure
2. Structure-Activity Relationships
3. Metabolic and Pharmacokinetic Properties
4. Toxicologic Effects
5. Short-Term Tests
6. Long-Term Animal Studies
7. Human Studies

In the Guidelines, the Long-Term Animal Studies section is covered in 25 column-inches, and the Human Studies section takes up about seven column-inches, an indication of the emphasis on long-term animal toxicology studies.

The evidence for the carcinogenicity of tobacco smoke is not based on long-term animal studies, which are negative. In this case, the strongest evidence is that obtained in a large number of epidemiologic studies of active smoking and lung cancer. The causality of the connection between inhalation of tobacco smoke and excess risk of lung cancer cannot be in doubt. It has been demonstrated that cessation of inhalation of tobacco smoke leads to a reduction of the excess lung cancer risk. The risk has been shown to be proportional to the amount of smoke inhaled. In terms of overall impact it has been shown that a very high proportion of the observed lung cancer incidence is due to inhalation of tobacco smoke. If the Guidelines for Carcinogenic Risk Assessment can be used to cast doubt on a finding that inhalation of tobacco smoke by humans causes an increased risk of lung cancer, the situation suggests a need to revise the Guidelines.

The inhalation of ETS by children, by non-smokers or former smokers represents a risk that is much smaller than that experienced by active smokers, but it is an involuntary exposure. It is not uncommon to derive quantitative risk assessments of exposures to carcinogens from data obtained in more heavily exposed occupational populations, and in that sense smokers represent a more heavily exposed population, providing data for extrapolation to the lower exposures imposed on children and adult non-smokers.

There are both differences and similarities in the characteristics and the composition of mainstream smoke, sidestream smoke, exhaled tobacco smoke and environmental tobacco smoke. It is important to deal both with the differences and similarities as they might affect the quantitative risk which is most accurately known for mainstream smoke. The difference in carcinogenic potential is not such that any one of these other categories could be considered as non-carcinogenic in humans. The very clear carcinogenicity of mainstream tobacco smoke directly implies carcinogenicity of ETS, particularly in view of the similarities in chemical composition and sizes of particulates between mainstream and sidestream smoke.

Meta-analyses of epidemiologic studies in non-smokers and former smokers are sensitive to decisions about exclusions and inclusions, and are primarily oriented towards increasing the overall statistical power and more precisely describing risk. Such analyses cannot effectively take into account any differences in quality of the study, differences in the way exposures were determined or classified, etc. Biases will be reduced only in that they will be averaged.

5.1.2 __Spousal Smoking__ All of the studies cited in the report on ETS and risk of lung cancer have made observations on married women who have been classified as "never-smoking". Those married to a smoker are assumed to be exposed to greater levels of ETS than those married to a nonsmoker (p.3-12). As noted in the report, this relative risk comparison implicitly compares women exposed to both spousal and other ETS to those exposed to other ETS only.

The ideal measure of ETS exposure for lung cancer studies would include all sources of ETS with data on both dose of ETS and exposure over time for a lifetime, or at a minimum over the past 20 to 30 years. Spousal smoking is believed to be a useful and valid marker for ETS exposure because (1) it often indicates many years of exposure (this contrasts with biological markers such as urinary cotinine, which indicate exposure at only one point in time); (2) the level of ETS exposure in the home when the spouse smokes appears to be greater in magnitude than the exposure from other, non-domestic, sources. Several studies exploring urinary cotinine as a measure of ETS exposure have found higher levels in non-smokers married to smoking spouses than to those married to nonsmoker spouses. The statement that ETS in the home is greater than that of other ETS exposures may be more or less true according to a variety of factors as noted below. The use of spousal smoking data is highly attractive because such data are easy and inexpensive to collect. For most studies spousal smoking is the only available measure of ETS exposure.

There are potential limitations in the use of spousal smoking as an indicator of ETS exposure that need to be considered:

1. Spousal smoking may account for a relatively small proportion of lifetime ETS exposure. Janerich et al. (1990) estimated that spousal exposure accounted for only 30% of lifetime exposure. These authors computed correlation coefficients of 0.37 and 0.51 between spousal smoking and lifetime ETS exposure for men and women, respectively. In this study childhood exposure was a major source of lifetime ETS exposure and correlated more highly with lifetime exposure. Likewise, Cummings et al. (1989) found little relationship between childhood, adult home and work place ETS exposure. On the other hand, Thompson and co-workers (1990) found that non-smokers who lived with a smoker reported more ETS exposure outside of the home than those who did not live with a smoker. In this way spousal smoking could be a more general indication of ETS exposure than

expected on the basis of exposure in the home per se, but sensitivity for total ETS exposure may vary among different study populations.

2. The results of comparing ETS household exposure to ETS household plus other exposures may vary in different countries and different regions within the U.S. Exposure within the residence depends on size and the type of construction of the dwelling, the amount of ventilation, and the proximity of smokers and nonsmokers within the home. Non-domestic background exposure varies with the nature of their workplace exposures, the extent of smoking restrictions in the work place and public places, the climate and the time of the year. With respect to the latter, exposures as assessed by urinary cotinine concentrations in Buffalo, New York were greater in the winter compared to the summer, presumably due to more time spent indoors with less ventilation in cold weather (Cummings et al., 1989). Such differences would be expected to be less marked in warmer regions of the country. For non-smoking people in particular, the extent of exposure outside of the home may depend on whether the woman works and how many other people in the population, who may be friends of non-smoking women, smoke. Thus, in countries such as Japan where fewer women work outside of the home, and fewer women in general smoke, spousal smoking may indicate differential exposure for women who are, and who are not exposed to ETS, than in the U.S. In any case, bias due to concerns (1) and (2) would decrease the difference in true exposure between the "exposed" and "non-exposed" non-smoking spouses, and would favor finding no difference in relative risk. These issues may explain some of the variability found in relative risk for lung cancer with ETS exposure in different countries around the world.

3. As noted previously, a major source of ETS exposure is that incurred in childhood, which could contribute to increased lung cancer risk in an adult. Although not generally specified in quantitating the risk of having a smoking spouse, it is possible that a person whose parent(s) smoked (and therefore who was exposed to ETS as a child) is more likely to marry a smoker. In this case the risk of ETS might

reflect the risk of combined childhood and spousal exposure rather than just exposure to the spouse.

4. The use of spousal smoking as an indicator of exposure may amplify the risk of misclassification of smokers as non-smokers. There appears to be a concordance between spousal smoking and false reporting of current or former smoking status. The misclassification of smoking status would falsely increase the relative risk of lung cancer in non-smokers related to ETS exposure. The misclassification issue is considered in detail in the report and appropriate corrections have been made for misclassification.

5. Spousal smoking status could be associated with several sources of potential confounding. For example, it is possible (although not documented by specific studies) that the presence of a smoking spouse is associated with an increased likelihood of lower socio-economic class, dietary differences, more alcohol or other drug exposure, more exposure to air pollution, etc. Such factors could possibly increase the risk of lung cancer, and published epidemiologic studies have addressed these factors to varying degrees. The potential sources of confounding based on spousal smoking status should be discussed in the report, with a recommendation that future studies explicitly address these issues.

In summary, considering its various limitations as an indicator of ETS exposure, spousal smoking status seems to be a reasonable method of identifying people with greater, versus lesser, ETS exposure. The problems in not accounting for background exposure would, if anything, bias against finding increased risk of lung cancer. Bias related to misclassification associated with smoking status has been addressed and corrected for in the draft report. There are possible confounders related to spousal smoking status, but such confounding concerns are present in other surrogates of exposure as well study. The importance of these confounders has not been determined to be sufficient to alter the conclusion that ETS increases the risk of lung cancer.

5.1.3 **United States and Foreign Studies** The Committee felt that data from studies conducted overseas as well as in the United States should be utilized in evaluating whether exposure to ETS increases risk of lung cancer. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted. The Committee commented that the text of Chapter 3 of the report seemed to overemphasize the Japanese cohort study, but felt that this and other non-U.S. investigations were directly relevant to establishing that ETS is a carcinogen for lung tissue.

Given the variety of study settings and the potential for differences in exposure to ETS between (and even within) countries, it is not surprising that relative risks vary from study to study. The higher relative risks found in some studies outside the United States may in part be related to differing characteristics of exposure to spousal smoking, differences in background ETS levels, or still other variables. The Committee believes that the report should recognize such potential differences, although adjustment for them may be precluded by lack of detailed ETS exposure data in the various studies. We do not disagree with the draft report's approach of incorporating data from around the world in estimating the numbers of lung cancer deaths in this country due to ETS, but believe that the estimates should be interpreted cautiously. In this regard, we recommend that the assumptions used, and their accompanying uncertainties in estimating numbers of lung cancer deaths attributable to ETS, be underscored.

5.1.4 Use of Meta-Analysis Meta-analysis is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS. However, the priority given the meta-analysis in this report in attempting to demonstrate that ETS is causally associated with lung cancer is not justified. Evidence on the carcinogenic effect of active smoking, the presence of carcinogens in ETS, and predicted lung cancer risk of low dose exposure to tobacco smoke from appropriate models, are an important part of establishing a causal relationship. The meta-analysis could then be interpreted as showing the available epidemiologic evidence is consistent with a small elevated risk.

Meta-analysis is a general term applied to a wide range of techniques whose objective is to synthesize findings across related studies. Although, there is still considerable debate over many aspects of conducting a meta-analysis, several criteria are usually considered essential. These include: 1) clear statement of the objective of the meta-analysis; 2) precise definition of criteria used to include (or exclude) studies; 3) critical review of studies included in the analysis; and 4) assessment of the effect of individual studies on the analysis. Many of these points were not adequately addressed in the meta-analysis provided in the EPA document.

The authors of the draft report did not provide a precise statement of the role of the meta-analysis. In regard to general methodology, there are several roles a meta-analysis might play. Bangert-Drowns (1986) distinguishes five different types of meta-analyses depending on the question to be addressed. In the EPA draft report, the consistency of the various studies is addressed, an attempt is made to estimate overall risk, the possibility of heterogeneity of study results is considered, and geographic variation is discussed as a possible source of heterogeneity. Unfortunately, it is not clear which of these issues is the primary target of the analysis. If it was intended to address all four issues, they were inadequately covered. In regard to consistency of findings (which is probably the most important issue), the findings were not presented in the most appropriate way. Estimates with corresponding confidence intervals are the most generally acceptable method of presentation. If the intention was to investigate heterogeneity, then formal tests of heterogeneity should have been provided. If it was intended to address the hypothesized U.S./foreign difference, it would have been useful to test the difference in risk between the two sub-groups of studies.

Specific criteria for including studies was not provided. The importance of this was reinforced at the Committee meeting when a reanalysis was presented on a different set of studies than those in the report. This resulted in a change in the overall risk estimate. Decisions as to study inclusion should be made prior to analysis, based on clearly stated criteria. It is also desirable to evaluate the impact on conclusions of closely related, but excluded, studies.

Finally, in testing the hypothesis of an elevated relative risk across studies, the reliance on the measure of "x-number of studies rejecting out of n" as the basis for the p-values seems somewhat arbitrary and inefficient. It would be preferable to use the sum of the S-statistics given in the report as a test statistic.

5.1.5 Confounders/Misclassification Important potential confounders of the ETS-lung cancer relationship were addressed in the report mainly by carrying out a separate meta-analysis of those studies which included adjusted analyses. The variables included in these adjusted analyses were age, education, and social class. Comparison of unadjusted and adjusted Rrs in those studies which present both, suggests that these variables are relatively unimportant.

There is no way to evaluate the importance of occupation, radon exposure, and diet as confounders of the ETS-lung cancer relationship, or to adjust for them, since virtually none of the studies contain information on them. However, they could be mentioned in the text as potential confounders.

The issue of misclassification should not be restricted to misclassification of current and ex-smokers as "never smokers." It should also be mentioned that non-differential misclassification of diagnosis (diagnoses other than lung cancer being incorrectly classified as lung cancer; or vice versa) will cause a biasing of the RR toward the null.

The misclassification of smoking status is differential in that current smokers and (particularly) ex-smokers are apt to be reported as "never smokers," whereas the reverse is unlikely.

The adjustment for misclassification of smokers as nonsmokers in the Report makes use of the formula used by the National Research Council for prospective studies, but no rationale or explanation for the formula is given in either Chapter 4 or Appendix B (Note also that several errors have been pointed out in the formulae given in Appendix B). Also, no distinction is made between prospective and case-control studies. In the latter, in order for bias due to misclassification of active smoking status to occur, there has to be differential misclassification between cases and controls.

Finally, not enough attention is given in the draft report to possible non-differential misclassification of ETS exposure. This is an important issue, since marriage to a smoking spouse is an imperfect proxy for total ETS exposure. In the case of dichotomous exposure, such misclassification would have the effect of biasing the RR estimate toward the null.

Other potential biases which deserve mention include recall bias (differential reporting of exposure status by cases compared to controls) and bias due to the use of proxy respondents.

5.1.6 **Characterization of Uncertainties** Vis-a-vis weight of evidence, the draft document's conclusion that exposure to ETS sometimes leads to the development of lung cancer in humans rests upon two main arguments: (1) the biological plausibility of such a causal association is high, given the known effects of active smoking and the known composition of ETS; and (2) the accumulating epidemiologic evidence on the relationship between exposure to ETS and lung cancer appears to argue for a positive effect. With exposure levels that are usually quite low, it is not surprising that the association is weak in many studies and in the aggregate, although, given the size of the exposed population, societally important. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great importance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

The biological plausibility argument depends upon establishing: (a) cigarette smoking's known carcinogenic effects; and (b) ETS's resemblance to mainstream tobacco smoke in terms of particle size distribution and composition of carcinogens, co-carcinogens and tumor promotors.

(a) Cigarette smoking's known effects. The document would benefit from a more complete presentation of the evidence concerning mainstream tobacco smoke's role in causing lung cancer. More detailed consideration of the dose-effect relationship for inhaled tobacco smoke would better set the stage for presenting evidence concerning the biological plausibility that exposure to ETS has similar, albeit lesser, health effects.

(b) ETS's resemblance to mainstream tobacco smoke. The ageing of tobacco smoke influences its uptake and deposition in the lung and its potential carcinogenicity. Nonetheless, there are strong similarities in the chemical and in vitro biological activity of ETS and mainstream tobacco smoke. These similarities should be discussed in

> the context of other complex mixtures, e.g., coke oven emissions, and diesel exhaust (The work of Lewtas at EPA should be revisited for this purpose). The uncertainties surrounding the evidence regarding changes in sidestream smoke composition should be assessed and the implications of such findings for the biological plausibility argument should be spelled out more thoroughly.

Epidemiologic evidence on the relationship between exposure to ETS and lung cancer should be described more completely, with the deficiencies of individual studies used to weight their contributions to any conclusions that are drawn. The assumptions and uncertainties associated with each step of the risk assessment process ought to be explicitly stated.

Not all the factors that probably contribute to the uncertainties surrounding the estimates of deaths attributable to ETS exposure are now considered. For example, it is important to justify the use of the particular biological marker chosen to estimate relative exposures (and, therefore, premature deaths) in passive versus active smokers, since that choice can cause the attributable deaths figure to vary over a twenty-fold range. Consequently, any estimate of the number of deaths to be expected each year from exposure to ETS should be justified more adequately than is now the case. A graphical presentation would clarify the uncertainties associated with each step as well as those inherent in the final estimate of attributable deaths.

As noted in Section 3.2, the cigarette-equivalent approach has a great advantage in that it is based on relatively sturdy RR determinations in active smokers, which can be used to project the risk (in the form of a percentage of the risk in active smokers) to nonsmokers exposed to ETS. However, the assessment of the cigarette-equivalent in non-smokers due to exposure to ETS has a considerable level of uncertainty embedded in it, i.e., about an order of magnitude. Neither cotinine nor smoke particulate levels are adequate direct indicators of carcinogenic components.

The other type of exposure assessment is based on inferences from the epidemiologic studies. Since spousal smoking is a very important exposure proxy used in many studies, there is concern about how usable this categorical classification is for quantitative exposure assessments. Physical proximity, daily length of exposure, and exposure outside the home to ETS may be quite different in different cultures and over decades of time. Misreporting of smoking status in the cases in some studies also introduces a bias. Various attempts have been made to apply corrections for these biases.

Both the relative potency approach and the cigarette equivalent approach share an implicit assumption that particle phase compounds, and polynuclear aromatic hydrocarbons in particular, are the carcinogens of interest. However, other carcinogens have been identified in ETS, and many of these are in the vapor phase (refer back to Section 3.7 for a full description). To the degree that vapor phase carcinogens have been ignored, or incompletely collected or extracted for experiments, the potency of ETS has been underestimated.

Another consideration is that the relative potency in animals is not necessarily the same as the relative potency in humans. The complexities of tobacco emissions complicate the cigarette equivalent approach. The referent mainstream emissions should be those of unfiltered cigarettes, upon which most of the active smoking epidemiologic data is based. The variable ratios in sidestream to mainstream emissions of toxins lead to differences in the calculated cigarette equivalents to which a passive smoker is exposed. These different emission ratios are one source of variability in the ratio of biomarkers in smokers and nonsmokers. For example, cotinine in nonsmokers is typically less than 1% of the level found in smokers, while the median level of 4-aminobiphenyl hemoglobin adducts in nonsmokers was 14% of the median in smokers. Furthermore, DNA adducts are subject to repair mechanisms, and the rate of repair may differ in smokers and nonsmokers.

5.1.7 Quantitative Risk Assessment The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis was a suitable approach to combining the data. This approach is the most direct and makes the fewest assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens and that those assessments are generally based on fewer studies.

Given that the epidemiology studies should be the basis of the risk assessment, some refinements of the risk assessment are recommended:

1. Criteria for Including Individual Studies in the Meta-analysis

   Criteria to include or exclude individual studies from the meta-analysis should be determined and explicitly stated (See section 5.1.4, preceding). The effects of individual excluded studies on the quantitative risk assessment should be evaluated and discussed. The power of the individual studies should also be considered and discussed.

2. Adjustment for Smoker Misclassification

   The rationale for the formula used to adjust for smoker misclassification should be given. Appropriate distinctions should be made in applying the misclassification formula to the case-control and the cohort studies. Because of the marriage aggregation factor -- the greater tendency for smokers to marry smokers -- the misclassification of some smokers as nonsmokers can artificially inflate the relative risk of lung cancer associated with passive smoking in cohort studies. In case control studies, misclassification by itself is not enough to inflate the relative risk. Differential misclassification, with cases mis-reporting more frequently than controls, is needed. The assumptions used in adjusting for smoker misclassification and their effect on the adjustment should be more fully discussed. If the approach taken is conservative, then it is noteworthy that the misclassification adjustment only lowers the relative risk estimate from a little over 1.4 to 1.3.

3. Misclassification of Exposure

   Some unexposed women, classified as un-exposed (non-smokers married to non-smokers) may in fact be exposed to relatively high levels of ETS in the workplace or in other settings outside of the home. Some recent of non-smokers' exposure to nicotine indicate variations in exposures ranging over two orders of magnitude. Correction for "background" exposure does not adequately correct for this misclassification. Furthermore, the use of spousal smoking habits to classify ETS exposure status is more likely to misclassify American women's exposure than Japanese women's exposure because of differences in American and Japanese lifestyles. Non-smoking American women married to non-smokers are more likely to be exposed to ETS outside of the home than are Japanese women because more American women work outside the home and have friends who smoke. Some evaluation of the effects of these biases would be appropriate in the risk estimations.

4. Uncertainties in the Estimate of Annual Lung Cancer Deaths Due to Passive Smoking

The uncertainty in the relative risk estimate of lung cancer due to passive smoking is based only on statistical considerations. There are other uncertainties that influence this estimate. A more critical analysis of the potential for systematic bias should be done. Acknowledging such uncertainties would provide greater balance to the report, while not substantially altering its overall message.

5. Dose-Response Estimation of Risk

There are many more assumptions and uncertainties in any risk estimation made on the basis of dose-response or dosimetry than for epidemiologic data. Nonetheless, such an estimate may be of value if the assumptions are fully stated and the uncertainties in the estimate are quantitatively estimated. With uncertainty estimates explicitly included, this approach may well be consistent with that based on epidemiology. Exposure estimates for ETS should include the exposures from birth to age 15, not only from age 15 on up as is done for mainstream smoking. This can have a substantial impact on the estimated risk. Complex dosimetry models should be considered the subject of research at this point in time, since they require many more assumptions.

6. Dose-Response Model for ETS-Radon Interaction Effects

Development of a specific dose-response model for ETS-radon interactions is not recommended. The interactions of ETS with radon are numerous and involve both physical and biological interactions which are not fully understood at present. Furthermore, there are no relevant epidemiological data concerning such interactions.

5.1.7 **Home vs. Workplace Exposure** The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace, and its importance in relation to total ETS exposure. However, the report should review and comment on the data that do exist, if only to bring out the need for future research in this area. The report should also review and comment on the data that exists on exposure to ETS in public places.

The Committee also recommends that EPA staff discuss possible approaches for estimating the exposure of children to ETS in homes with one or more smoking parents. This is recommended because of the potentially large public health impact of respiratory disorders in children that may be caused by exposure to ETS. Careful consideration should be given to the differences in the exposure parameters required for lung cancer as opposed to respiratory disorder assessments. For example, cancer assessment may require integrating exposures over longer time intervals than does the assessment of respiratory disorders. Besides developing approaches for estimating average child population exposures, it is also important to establish the shape of the exposure distribution, particularly the tail of the distribution, in order to determine whether a numerically significant subset of children is at high risk.

5.2 Respiratory Disorders in Children

Chapter 5 on respiratory disorders in children was a commendable first effort for a very difficult task. Nevertheless, we found that it could be substantively improved and that the conclusions drawn could be made much stronger if the chapter is revised in the manner suggested in Section 3.3.

The Committee found the evidence for respiratory health effects in children to be stronger and more persuasive than stated in Chapter 5 of the draft ETS Risk Assessment document, and recommends that the new draft contain a chapter devoted to quantitative risk assessment, in terms of the number of children at risk for various outcomes. It would be analogous to Chapter 4, which deals only with the evidence for lung cancer risk discussed in Chapter 3. The risks are different, but it is possible that the impact of ETS on respiratory health in children may have much greater public health significance than the impacts of ETS on lung cancer in nonsmokers.

There will need to be new material in the earlier chapters on lung dosimetry and the physical and chemical factors affecting it. The difference in deposition and retention of ETS components between children and adults need to be recognized and considered in a risk assessment.

5.2.1 **Weight of Evidence** The scope of Chapter 5 is limited to selected studies published subsequent to the 1986 Surgeon General's Report and the National Research Council Report. Neither of these reports judged the associations of ETS exposure and children with adverse respiratory effects to be causal; alternative explanations for the associations including confounding and information bias could not be excluded. The additional literature available since 1986 provides a basis for increased concern. Thus, the Committee urges a thorough review of the entire body of evidence. A considered judgment cannot be made concerning causality without assessing the totality of the evidence including studies reviewed in the two 1986 reports and those published subsequently.

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed (causality, confounding, information bias) and the individual studies reviewed for the approaches used to address confounding and information bias. The weight of the evidence could then be judged to determine the causality of associations.

With regard to including the reviews of the 26 new reports as Appendix E, the scope of the review should be expanded to include all studies not in the 1986 Surgeon General's Report. A more comprehensive search is needed since the 26 publications identified by the chapter's authors do not represent all significant publications on the effects of ETS on children published since 1986.

5.2.2 **Confounders** A number of confounders were mentioned by the report, but addressed improperly. These include in utero exposure, parental reporting bias, and active smoking. The Committee considers the following factors to be critical:

- Unreported Smoking
- Other Indoor Pollutants
- Biological Precursors & Medical Characteristics
- Exposure to Biological Agents
- Other Exposures (outdoor)
- Parental Symptoms
- Socio-Economic Factors
- Other Sources of Reporting Bias (includes Annoyance Responses)

One must stress the biological precursors important to the effects of ETS in childhood. These include genetic predisposition (physiological, immunological and biochemical), _in utero_ exposure, and breast feeding. These also include environmentally-induced atopy and residua of infections. Pre-existing medical conditions, such as cystic fibrosis, congenital defects will also affect responses to ETS.

The socio-economic and behavioral factors are important as they relate to nutrition (re: resistance), familial crowding, and other contacts (especially day care), medical attitudes and medical care, etc. Socio-economic status (SES) and day care have been shown to modify the effects of ETS.

Reporting bias is a critical issue for ascertaining exposure, as has been documented by many previously. There are two major components to this, the positive bias and the negative bias. The first is thought to occur associated with parental conditions (e.g., Colley, 1974; Cederlof and Colley, 1974). The second is thought to occur because the respondent becomes annoyed by ETS (e.g., Weber 1984; Hugod 19 84; NCHS 1976; NIOSH 1971), and/or have anger/aggression reactions (e.g., Jones and Bogat 1978).

Effects of active/self-smoking interacting with passive smoking should be discussed (Bland et al. 19 78; Lebowitz et al. 1987 and 1988)

Other exposures which have similar effects (e.g., wood smoke, other particulate matter, NO_2, formaldehyde) may be confounding the effects of ETS (Hammer et al. 1976; Anderson 1979; Speizer et al. 1980 (with update); Comstock et al. 1981; Melia et al. 1982; and Koo et al. 1988), or may interact with ETS in producing effects (Lebowitz et al. 1990, and in press). Of course, individuals including children may have multiple micro-environments in which they are exposed, so insufficient information would tend to yield incorrect exposure-response curves.

Thus, there are many possible co-variates and confounders which should still be considered (Lebowitz 1990).

5.2.3 **Use of Meta-Analysis** The staff should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there is a body of suitable studies for such an analysis. If one is warranted, it should be guided, to the extent possible, by the same considerations outlined in Section 5.1.4.

6.0 SUMMARY AND CONCLUSIONS

In conducting its review of the ETS Risk Assessment document and Policy Guide, the Committee found them to be good faith efforts to address complex and difficult issues affecting public health. The authors attempted to select and interpret the most relevant information from an enormous and diverse scientific data base, most of which was not designed or intended to yield the information needed for this task. Since the task is extremely difficult, it should come as no surprise that the Committee also found the documents to be incomplete in many respects. The situation is analogous to that for the Criteria Air Pollutants, where it has been necessary to prepare and review two or more draft documents prior to their endorsement by the Clean Air Scientific Advisory Committee (CASAC). This Committee has suggested both organizational and specific technical changes and additional analyses that, if followed, can result in improved ETS Risk Assessment and Policy Guide documents, and stands ready to provide further review comments on the revised drafts.

The SAB was asked to address the following issues in reviewing the documents:

A. Lung Cancer in Adults The Committee noted that Chapters 3 and 4 addressed only the issue of lung cancer risk for non-smoking women due to spousal smoking. The revised document should be expanded to include the full range of cancer impacts of ETS. The Committee also noted a number of areas where substantial improvements could be made organizationally, and in terms of content of material that was not adequately covered or not covered at all, and urge the EPA staff to redraft those chapters as well. Comments on specific issues within the broader context of lung cancer follow below.

1. Carcinogenicity of ETS The Committee concurs with the judgement of EPA that Environmental Tobacco Smoke should be classified as a Class A Carcinogen. The Committee had some difficulty with the use of the Guidelines for Carcinogen Risk Assessment as they are currently formulated (51 FR 33992 August 22, 1986).

The strongest evidence for the carcinogenicity of tobacco smoke is that obtained in a large number of epidemiologic studies of smoking and lung cancer. The causality of the connection between direct inhalation of tobacco smoke and excess risk of lung cancer cannot be in doubt. It has been demonstrated that cessation of inhalation of tobacco smoke leads to a reduction of the excess lung cancer risk. The risk has been shown to be proportional to the amount of smoke inhaled. In terms of overall impact it has been shown that a very high proportion of the current lung cancer incidence is due to inhalation of tobacco smoke. The ageing of sidestream tobacco smoke influences its uptake and deposition in the lung and its potential carcinogenicity, but there are strong similarities in the chemical and in vitro biological activity of ETS and mainstream tobacco smoke, and ETS resembles mainstream tobacco smoke in terms of particle size distribution and composition of carcinogens, co-carcinogens and tumor promotors.

The inhalation of ETS by children, by non-smokers or former smokers represents a risk that is much smaller than that experienced by smokers, but it is an involuntary exposure. It is not uncommon to derive quantitative risk assessments of exposures to carcinogens from data obtained in more heavily exposed occupational populations, and in that sense smokers represent a more heavily exposed population which can be used for extrapolation to the lower exposures imposed on children and non-smokers.

2. Spousal Smoking All of the studies cited in the report on ETS and risk of lung cancer have made observations on married women who have been classified as "never-smoking." Those married to a smoker are assumed to be exposed to greater levels of ETS than those married to a nonsmoker. As noted in the report, this relative risk comparison is implicitly a comparison of women exposed to both spousal and other ETS to those exposed to other ETS only.

Spousal smoking is believed to be a useful maker for total ETS exposure because (1) it often indicates many years of exposure: this contrasts with biological markers such as urinary cotinine, which indicate exposure at only one point in time; (2) the level of ETS exposure in the home when the spouse smokes appears to be of substantially greater magnitude than the background exposure.

There are potential limitations in the use of spousal smoking as an indicator of ETS exposure that need to be considered:

1. Spousal smoking may account for a relatively small proportion of lifetime ETS exposure.

2. The difference in ETS exposure comparing household exposure versus household plus background exposure may differ in different countries and different regions within the U.S.

3. A major source of ETS exposure is that incurred in childhood, which could contribute to increased lung cancer risk in an adult.

4. The use of spousal smoking as an indicator of exposure may amplify the risk of misclassification of smokers as nonsmokers.

5. Spousal smoking status could be associated with several sources of confounding, e.g., lower socio-economic class, diet, alcohol, drugs, more exposure to air pollution, etc., factors that could possibly increase lung cancer risk.

Despite various limitations as an indicator of ETS exposure, spousal smoking status is a reasonable method of identifying people with greater, versus lesser, ETS exposure.

3. **United States and Foreign Studies** The Committee felt that data from studies conducted overseas as well as in the United States should be utilized in evaluating whether exposure to ETS increases risk of lung cancer. It is appropriate to examine the totality of evidence from all the case-control and cohort studies, regardless of where they were conducted.

4. **Use of Meta-Analysis** Meta-analysis is an appropriate tool to summarize the epidemiological studies investigating the risk of ETS. However, the priority given the meta-analysis in this report in attempting to demonstrate that ETS is causally associated with lung cancer is not justified. Evidence on the carcinogenic effect of active smoking, the presence of carcinogens in ETS, and predicted lung cancer risk of low dose exposure to tobacco smoke from appropriate models are an important part of establishing a causal relationship. The meta-analysis could then be interpreted as showing the available epidemiologic evidence is consistent with a small elevated risk.

5. Confounders/Misclassification Important potential confounders of the ETS-lung cancer relationship were addressed in the Report mainly by carrying out a separate meta-analysis of those studies which included adjusted analyses. The main confounders included in these adjusted analyses were: age, education, and social class. Comparison of unadjusted and adjusted RRs in those studies which present both, suggests that these variables are not important confounders.

As for other potential confounders of the ETS-lung cancer relationship, including occupation, radon exposure, and diet, there is no way to evaluate their importance as confounders or to adjust for them, since virtually none of the studies contains information on them. However, they could be mentioned in the text as potential confounders.

The issue of misclassification should not be restricted to misclassification of current and ex-smokers as "never smokers." It should also be mentioned that misclassification of diagnosis (diagnoses other than lung cancer being incorrectly classified as lung cancer; or vice versa) will cause a biasing of the RR toward the null.

Not enough attention was given to possible non-differential misclassification of ETS exposure. This is an important issue, since marriage to a smoking spouse is an imperfect proxy for total ETS exposure. In the case of dichotomous exposure, such misclassification would have the effect of biasing the RR estimate toward the null. Other potential biases which deserve mention include recall bias (differential reporting of exposure status by cases compared to controls) and bias due to the use of proxy respondents.

6. Characterization of Uncertainties The draft risk assessment document's findings on the ETS/adult lung cancer relationship is based on two main arguments: (1) biological plausibility; and (2) epidemiologic evidence. With exposure levels that are usually quite low, it is not surprising that the association is likely to be weak although, given the size of the exposed population, societally important. Because the epidemiologic evidentiary base for drawing conclusions regarding ETS's carcinogenicity consists mainly of studies of exposure levels produced by spousal smoking, the biological plausibility argument assumes great impor-

tance. Each step in that argument should therefore be carefully addressed, with the uncertainties encountered being spelled out explicitly.

7. **Quantitative Risk Assessment** The Committee generally agreed that the quantitative assessment of the risk of lung cancer due to exposures to ETS should be based on the human epidemiology studies and that meta-analysis was a suitable approach to combining the data. It is direct and makes few assumptions. It should be noted that this approach is fully consistent with the risk assessments that have been done for many other carcinogens and that those assessments are generally based on fewer studies.

Given that the epidemiology studies should be the basis of the risk assessment, some refinements of the risk assessment are recommended with respect to:

1. Criteria for Including Individual Studies in the Meta-analysis
2. Adjustment for Smoker Misclassification
3. Misclassification of Exposure
4. Uncertainties in the Estimate of Annual Lung Cancer Deaths Due to Passive Smoking
5. Dose-Response Estimation of Risk

8. **Home vs. Workplace Exposure** The Committee recognizes that there is little epidemiologic literature on the health effects of ETS in the workplace. However, the report should review and comment on the data that do exist.

B. **Respiratory Disorders in Children** Chapter 5 on respiratory disorders in children was a commendable first effort for a very difficult task. Nevertheless, we found that it could be substantially improved and that the conclusions drawn in it could be made much stronger if the chapter was revised in the manner suggested in this report.

The Committee found the evidence for respiratory health effects in children to be stronger and more persuasive than that stated in Chapter 5 of the draft ETS Risk Assessment document, and recommends that the new draft contain a chapter devoted to quantitative risk assessment. It would be analogous to Chapter 4, which deals only with the evidence for lung cancer risk discussed in Chapter 3. The risks are different, but it is possible that the impact of ETS on respiratory health in children may have much greater public health significance than the impact of ETS on lung cancer in nonsmokers.

The earlier chapters on lung dosimetry and the physical and chemical factors affecting it should incorporate new material. The difference in deposition and retention of ETS components between children and adults need to be established and considered in a risk assessment.

Comments om specific issues follow:

1. **Weight of Evidence** The scope of Chapter 5 is limited to selected studies published subsequent to the 1986 Surgeon General's Report and the National Research Council Report. The additional literature available since 1986 provides a basis for increased concern. Thus, the Committee urges a thorough review of the entire body of evidence. Judgment cannot be made concerning causality without assessing the totality of the evidence including studies reviewed in the two 1986 reports and those published subsequently.

In reviewing the weight of the evidence, the present Chapter 5 does not establish an appropriate framework for considering the data. The alternative explanations for association of ETS exposure with adverse respiratory effects need to be clearly listed (causality, confounding, information bias) and the individual studies reviewed for the approaches used to address confounding and information bias. The weight of the evidence could then be judged to determine the causality of associations.

2. **Confounders** A number of confounders were mentioned by the report, but addressed improperly, such as in utero exposure, parental reporting bias, and active smoking.

The biological precursors important to the effects of ETS in childhood include genetic predisposition (physiological, immunological and biochemical), in utero exposure, and breast feeding. These also include environmentally-induced atopy and residua of infections. Pre-existing medical conditions, such as cystic fibrosis, congenital defects will also affect responses to ETS.

The socio-economic and behavioral factors are important as they relate to nutrition (re: resistance), familial crowding and other contacts (especially day care), medical attitudes and medical care, etc. SES and day care have been shown to modify effects of ETS.

3. Use of Meta-Analysis The staff should give serious consideration to meta-analysis of those studies of sufficiently similar design to warrant it. However, it was not clear that there was a body of suitable studies for such an analysis. If one is warranted, it should be guided, to the extent possible, by the same considerations outlined for meta-analysis for lung cancer.

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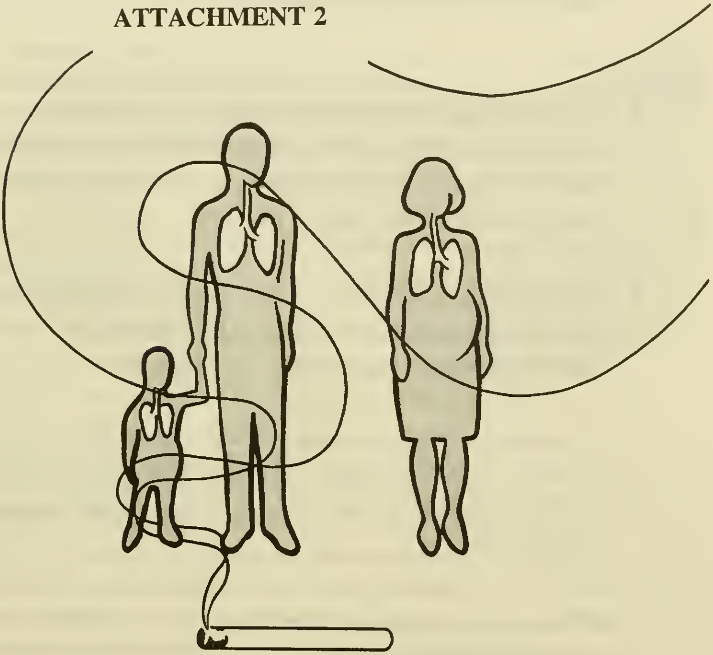
EPA/600/6-90/006F
December 1992

Respiratory Health Effects of Passive Smoking:

Lung Cancer and Other Disorders

ATTACHMENT 2



Note: The following has been excerpted from the above named document.

1. SUMMARY AND CONCLUSIONS

1.1. MAJOR CONCLUSIONS

Based on the weight of the available scientific evidence, the U.S. Environmental Protection Agency (EPA) has concluded that the widespread exposure to environmental tobacco smoke (ETS) in the United States presents a serious and substantial public health impact.

In adults:

- ETS is a human lung carcinogen, responsible for approximately 3,000 lung cancer deaths annually in U.S. nonsmokers.

In children:

- ETS exposure is causally associated with an increased risk of lower respiratory tract infections (LRIs) such as bronchitis and pneumonia. This report estimates that 150,000 to 300,000 cases annually in infants and young children up to 18 months of age are attributable to ETS.

- ETS exposure is causally associated with increased prevalence of fluid in the middle ear, symptoms of upper respiratory tract irritation, and a small but significant reduction in lung function.

- ETS exposure is causally associated with additional episodes and increased severity of symptoms in children with asthma. This report estimates that 200,000 to 1,000,000 asthmatic children have their condition worsened by exposure to ETS.

- ETS exposure is a risk factor for new cases of asthma in children who have not previously displayed symptoms.

1.2. BACKGROUND

Tobacco smoking has long been recognized (e.g., U.S. Department of Health, Education, and Welfare [U.S. DHEW], 1964) as a major cause of mortality and morbidity, responsible for an estimated 434,000 deaths per year in the United States (Centers for Disease Control [CDC], 1991a). Tobacco use is known to cause cancer at various sites, in particular the lung (U.S. Department of Health and Human Services [U.S. DHHS], 1982; International Agency for Research on Cancer [IARC], 1986). Smoking can also cause respiratory diseases (U.S. DHHS, 1984, 1989) and is a major risk factor for heart disease (U.S. DHHS, 1983). In recent years, there has been concern that nonsmokers may also be at risk for some of these health effects as a result of their exposure ("passive smoking") to the tobacco smoke that occurs in various environments occupied by smokers. Although this ETS is dilute compared with the mainstream smoke (MS) inhaled by active smokers, it is chemically similar, containing many of the same carcinogenic and toxic agents.

In 1986, the National Research Council (NRC) and the Surgeon General of the U.S. Public Health Service independently assessed the health effects of exposure to ETS (NRC, 1986; U.S. DHHS, 1986). Both of the 1986 reports conclude that ETS can cause lung cancer in adult nonsmokers and that children of parents who smoke have increased frequency of respiratory symptoms and acute lower respiratory tract infections, as well as evidence of reduced lung function.

More recent epidemiologic studies of the potential associations between ETS and lung cancer in nonsmoking adults and between ETS and noncancer respiratory effects more than double the size of the database available for analysis from that of the 1986 reports. This EPA report critically reviews the current database on the respiratory health effects of passive smoking; these data are utilized to develop a hazard identification for ETS and to make quantitative estimates of the public health impacts of ETS for lung cancer and various other respiratory diseases.

The weight-of-evidence analysis for the lung cancer hazard identification is developed in accordance with U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a) and established principles for evaluating epidemiologic studies. The analysis considers animal bioassays and genotoxicity studies, as well as biological measurements of human uptake of tobacco smoke components and epidemiologic data on active and passive smoking. The availability of abundant and consistent human data, especially human data at actual environmental levels of exposure to the specific agent (mixture) of concern, allows a hazard identification to be made with a high degree of certainty. The conclusive evidence of the dose-related lung carcinogenicity of

MS in active smokers (Chapter 4), coupled with information on the chemical similarities of MS and ETS and evidence of ETS uptake in nonsmokers (Chapter 3), is sufficient by itself to establish ETS as a known human lung carcinogen, or "Group A" carcinogen under U.S. EPA's carcinogen classification system. In addition, this document concludes that the overall results of 30 epidemiologic studies on lung cancer and passive smoking (Chapter 5), using spousal smoking as a surrogate of ETS exposure for female never-smokers, similarly justify a Group A classification.

The weight-of-evidence analyses for the noncancer respiratory effects are based primarily on a review of epidemiologic studies (Chapter 7). Most of the endpoints examined are respiratory disorders in children, where parental smoking is used as a surrogate of ETS exposure. For the noncancer respiratory effects in nonsmoking adults, most studies used spousal smoking as an exposure surrogate. A causal association was concluded to exist for a number of respiratory disorders where there was sufficient consistent evidence for a biologically plausible association with ETS that could not be explained by bias, confounding, or chance. The fact that the database consists of human evidence from actual environmental exposure levels gives a high degree of confidence in this conclusion. Where there was suggestive but inconclusive evidence of causality, as was the case for asthma induction in children, ETS was concluded to be a risk factor for that endpoint. Where data were inconsistent or inadequate for evaluation of an association, as for acute upper respiratory tract infections and acute middle ear infections in children, no conclusions were drawn.

This report also has attempted to provide estimates of the extent of the public health impact, where appropriate, in terms of numbers of ETS-attributable cases in nonsmoking subpopulations. Unlike for qualitative hazard identification assessments, where information from many sources adds to the confidence in a weight-of-evidence conclusion, for quantitative risk assessments, the usefulness of studies usually depends on how closely the study population resembles nonsmoking segments of the general population. For lung cancer estimates among U.S. nonsmokers, the substantial epidemiology database of ETS and lung cancer among U.S. female never-smokers was considered to provide the most appropriate information. From these U.S. epidemiology studies, a pooled relative risk estimate was calculated and used in the derivation of the population risk estimates. The large number of studies available, the generally consistent results, and the condition of actual environmental levels of exposure increase the confidence in these estimates. Even under these circumstances, however, uncertainties remain, such as in the use of questionnaires and current biomarker measurements to estimate past exposure, assumptions of exposure-response linearity, and extrapolation to male never-smokers and to ex-smokers. Still, given the strength of the evidence for the lung carcinogenicity of tobacco smoke and the extensive human database from actual environmental exposure levels, fewer assumptions are necessary than is usual in EPA quantitative risk assessments, and confidence in these estimates is rated medium to high.

Population estimates of ETS health impacts are also made for certain noncancer respiratory endpoints in children, specifically lower respiratory tract infections (i.e., pneumonia, bronchitis, and bronchiolitis) and episodes and severity of attacks of asthma. Estimates of ETS-attributable cases of LRI in infants and young children are thought to have a high degree of confidence because of the consistent study findings and the appropriateness of parental smoking as a surrogate measure of exposure in very young children. Estimates of the number of asthmatic children whose condition is aggravated by exposure to ETS are less certain than those for LRIs because of different measures of outcome in various studies and because of increased extraparental exposure to ETS in older children. Estimates of the number of new cases of asthma in previously asymptomatic children also have less confidence because at this time the weight of evidence for asthma induction, while suggestive of a causal association, is not conclusive.

Most of the ETS population impact estimates are presented in terms of ranges, which are thought to reflect reasonable assumptions about the estimates of parameters and variables required for the extrapolation models. The validity of the ranges is also dependent on the appropriateness of the extrapolation models themselves.

While this report focuses only on the respiratory health effects of passive smoking, there also may be other health effects of concern. Recent analyses of more than a dozen epidemiology and toxicology studies (e.g., Steenland, 1992; National Institute for Occupational Safety and Health [NIOSH], 1991) suggest that ETS exposure may be a risk factor for cardiovascular disease. In addition, a few studies in the literature link ETS exposure to cancers of other sites; at this time, that database appears inadequate for any conclusion. This report does not develop an analysis of either the nonrespiratory cancer or the heart disease data and takes no position on whether ETS is a risk factor for these diseases. If it is, the total public health impact from ETS will be greater than that discussed here.

1.3. PRIMARY FINDINGS

A. Lung Cancer in Nonsmoking Adults

1. Passive smoking is causally associated with lung cancer in adults, and ETS, by the total weight of evidence, belongs in the category of compounds classified by EPA as Group A (known human) carcinogens.
2. Approximately 3,000 lung cancer deaths per year among nonsmokers (never-smokers and former smokers) of both sexes are estimated to be attributable to ETS in the United States. While there are statistical and modeling uncertainties

in this estimate, and the true number may be higher or lower, the assumptions used in this analysis would tend to underestimate the actual population risk. The overall confidence in this estimate is medium to high.

B. Noncancer Respiratory Diseases and Disorders

1. Exposure of children to ETS from parental smoking is causally associated with:
    a. increased prevalence of respiratory symptoms of irritation (cough, sputum, and wheeze),
    b. increased prevalence of middle ear effusion (a sign of middle ear disease), and
    c. a small but statistically significant reduction in lung function as tested by objective measures of lung capacity.
2. ETS exposure of young children and particularly infants from parental (and especially mother's) smoking is causally associated with an increased risk of LRIs (pneumonia, bronchitis, and bronchiolitis). This report estimates that exposure to ETS contributes 150,000 to 300,000 LRIs annually in infants and children less than 18 months of age, resulting in 7,500 to 15,000 hospitalizations. The confidence in the estimates of LRIs is high. Increased risks for LRIs continue, but are lower in magnitude, for children until about age 3; however, no estimates are derived for children over 18 months.
3. a. Exposure to ETS is causally associated with additional episodes and increased severity of asthma in children who already have the disease. This report estimates that ETS exposure exacerbates symptoms in approximately 20% of this country's 2 million to 5 million asthmatic children and is a major aggravating factor in approximately 10%.
    b. In addition, the epidemiologic evidence is suggestive but not conclusive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms. Based on this evidence and the known ETS effects on both the immune system and lungs (e.g., atopy and airway hyperresponsiveness), this report concludes that ETS is a risk factor for the induction of asthma in previously asymptomatic children. Data suggest that relatively high levels of exposure are required to induce new cases of asthma in children. This report calculates that previously asymptomatic children exposed to ETS from mothers who smoke at least 10 cigarettes per day will exhibit an estimated 8,000 to 26,000 new cases of

asthma annually. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

4. Passive smoking has subtle but significant effects on the respiratory health of nonsmoking adults, including coughing, phlegm production, chest discomfort, and reduced lung function.

This report also has reviewed data on the relationship of maternal smoking and sudden infant death syndrome (SIDS), which is thought to involve some unknown respiratory pathogenesis. The report concludes that while there is strong evidence that infants whose mothers smoke are at an increased risk of dying from SIDS, available studies do not allow us to differentiate whether and to what extent this increase is related to in utero versus postnatal exposure to tobacco smoke products. Consequently, this report is unable to assert whether or not ETS exposure by itself is a risk factor for SIDS independent of smoking during pregnancy.

Regarding an association of parental smoking with either upper respiratory tract infections (colds and sore throats) or acute middle ear infections in children, this report finds the evidence inconclusive.

1.3.1. ETS and Lung Cancer

1.3.1.1. *Hazard Identification*

The Surgeon General (U.S. DHHS, 1989) estimated that smoking was responsible for more than one of every six deaths in the United States and that it accounted for about 90% of the lung cancer deaths in males and about 80% in females in 1985. Smokers, however, are not the only ones exposed to tobacco smoke. The sidestream smoke (SS) emitted from a smoldering cigarette between puffs (the main component of ETS) has been documented to contain virtually all of the same carcinogenic compounds (known and suspected human and animal carcinogens) that have been identified in the mainstream smoke (MS) inhaled by smokers (Chapter 3). Exposure concentrations of these carcinogens to passive smokers are variable but much lower than for active smokers. An excess cancer risk from passive smoking, however, is biologically plausible.

Based on the firmly established causal association of lung cancer with active smoking with a dose-response relationship down to low doses (Chapter 4), passive smoking is considered likely to affect the lung similarly. The widespread presence of ETS in both home and workplace and its absorption by nonsmokers in the general population have been well documented by air sampling and by body measurement of biomarkers such as nicotine and cotinine (Chapter 3). This raises the question of whether any direct evidence exists for the relationship between ETS exposure and lung cancer in the general population and what its implications may be for public health. This report addresses that question by reviewing and analyzing the evidence from 30 epidemiologic studies of effects from normally occurring environmental levels of ETS (Chapter 5). Because there is widespread exposure and it is difficult to construct a truly unexposed subgroup of the general population, these studies attempt to compare individuals with higher ETS exposure to those with lower exposures. Typically, female never-smokers who are married to a smoker are compared with female never-smokers who are married to a nonsmoker. Some studies also consider ETS exposure of other subjects (i.e., male never-smokers and long-term former smokers of either sex) and from other sources (e.g., workplace and home exposure during childhood), but these studies are fewer and represent fewer cases, and they are generally excluded from the analysis presented here. Use of the female never-smoker studies provides the largest, most homogeneous database for analysis to determine whether an ETS effect on lung cancer is present. This report assumes that the results for female never-smokers are generalizable to all nonsmokers.

Given that ETS exposures are at actual environmental levels and that the comparison groups are both exposed to appreciable background (i.e., nonspousal) ETS, any excess risk for lung cancer from exposure to spousal smoke would be expected to be small. Furthermore, the risk of lung cancer is relatively low in nonsmokers, and most studies have a small sample size, resulting in a very low statistical power (probability of detecting a real effect if it exists). Besides small sample size and low incremental exposures, other problems inherent in several of the studies may also limit their ability to detect a possible effect. Therefore, this report examines the data in several different ways. After downward adjustment of the relative risks for smoker misclassification bias, the studies are individually assessed for strength of association, both for the overall data and for the highest exposure group when exposure-level data are available, and for exposure-response trend. Then the study results are pooled by country using statistical techniques for combining data, including both positive and nonpositive results, to increase the ability to determine whether or not there is an association between ETS and lung cancer. Finally, in addition to the previous statistical analyses that weight the studies only by size, regardless of design and conduct, the studies are qualitatively evaluated for potential confounding, bias, and likely utility to provide information about any lung carcinogenicity of ETS. Based on these qualitative considerations, the studies are categorized into one of four tiers and then statistically analyzed successively by tier.

Results from all of the analyses described above strongly support a causal association between lung cancer ETS exposure. The overall proportion (9/30) of individual studies found to show an association between lung cancer and spousal ETS exposure at all levels combined is unlikely to occur by chance ($p < 10^{-4}$). When the analysis focuses on higher levels of spousal exposure, every one of the 17 studies with exposure-level data shows increased risk in the highest exposure group; 9 of these are significant at the $p < 0.05$ level, despite most having low power, another result highly unlikely to occur by chance ($p < 10^{-7}$). Similarly, the proportion (10/14; $p < 10^{-9}$) showing a statistically significant exposure-response trend is highly supportive of a causal association.

Combined results by country showed statistically significant associations for Greece (2 studies), Hong Kong (4 studies), Japan (5 studies), and the United States (11 studies), and in that order of strength of relative risk. Pooled results of the four Western European studies (three countries) actually showed a slightly stronger association than that of the United States, but it was not statistically significant, probably due to the smaller sample size. The combined results of the Chinese studies do not show an association between ETS and lung cancer; however, two of the four Chinese studies were designed mainly to determine the lung cancer effects of high levels of other indoor air pollutants indigenous to those areas, which would obscure a smaller ETS effect. These two Chinese studies do, however, provide very strong evidence on the lung carcinogenicity of these other indoor air pollutants, which contain many of the same components as ETS. When results are combined only for the other two Chinese studies, they demonstrate a statistically significant association for ETS and lung cancer.

The heterogeneity of observed relative risk estimates among countries could result from several factors. For example, the observed differences may reflect true differences in lung cancer rates for never-smokers, in ETS exposure levels from nonspousal sources, or in related lifestyle characteristics in different countries. For the time period in which ETS exposure was of interest for these studies, spousal smoking is considered to be a better surrogate for ETS exposure in more "traditional" societies, such as Japan and Greece, than in the United States. In the United States, other sources of ETS exposure (e.g., work and public places) are generally higher, which obscures the effects of spousal smoking and may explain the lower relative risks observed in the United States. Nevertheless, despite observed differences between countries, all showed evidence of increased risk.

Based on these analyses and following the U.S. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), EPA concludes that environmental tobacco smoke is a Group A (known human) carcinogen. This conclusion is based on a total weight of evidence, principally:

- Biological plausibility. ETS is taken up by the lungs, and components are distributed throughout the body. The presence of the same carcinogens in ETS and MS, along with the established causal relationship between lung cancer and active smoking with the dose-response relationships exhibited down to low doses, establishes the plausibility that ETS is also a lung carcinogen.

- Supporting evidence from animal bioassays and genotoxicity experiments. The carcinogenicity of tobacco smoke has been demonstrated in lifetime inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of SS condensates has been shown in intrapulmonary implantations and skin painting experiments. Positive results of genotoxicity testing for both MS and ETS provide corroborative evidence for their carcinogenic potential.
- Consistency of response. All 4 of the cohort studies and 20 of the 26 case-control studies observed a higher risk of lung cancer among the female never-smokers classified as ever exposed to any level of spousal ETS. Furthermore, every one of the 17 studies with response categorized by exposure level demonstrated increased risk for the highest exposure group. When assessment was restricted to the 19 studies judged to be of higher utility based on study design, execution, and analysis (Appendix A), 17 observed higher risks, and 6 of these increases were statistically significant, despite most having low statistical power. Evaluation of the total study evidence from several perspectives leads to the conclusion that the observed association between ETS exposure and increased lung cancer occurrence is not attributable to chance.
- Broad-based evidence. These 30 studies provide data from 8 different countries, employ a wide variety of study designs and protocols, and are conducted by many different research teams. Results from all countries, with the possible exception of two areas of China where high levels of other indoor air lung carcinogens were present, show small to modest increases in lung cancer associated with spousal ETS exposure. No alternative explanatory variables for the observed association between ETS and lung cancer have been indicated that would be broadly applicable across studies.
- Upward trend in exposure-response. Both the largest of the cohort studies--the Japanese study of Hirayama with 200 lung cancer cases--and the largest of the case-control studies--the U.S. study by Fontham and associates (1991) with 420 lung cancer cases and two sets of controls--demonstrate a strong exposure-related statistical association between passive smoking and lung cancer. This upward trend is well supported by the preponderance of epidemiology studies. Of the 14 studies that provide sufficient data for a trend test by exposure level, 10 were statistically significant despite most having low statistical power.
- Detectable association at environmental exposure levels. Within the population of married women who are lifelong nonsmokers, the excess lung cancer risk from

exposure to their smoking husbands' ETS is large enough to be observed, even for all levels of their spousal exposure combined. Carcinogenic responses are usually detectable only in high-exposure circumstances, such as occupational settings, or in experimental animals receiving very high doses. In addition, effects are harder to observe when there is substantial background exposure in the comparison groups, as is the case here.

- Effects remain after adjustment for potential upward bias. Current and ex-smokers may be misreported as never-smokers, thus inflating the apparent cancer risk for ETS exposure. The evidence remains statistically significant and conclusive, however, after adjustments for smoker misclassification. For the United States, the summary estimate of relative risk from nine case-control plus two cohort studies is 1.19 (90% confidence interval [C.I.] = 1.04, 1.35; $p < 0.05$) after adjustment for smoker misclassification. For Greece, 2.00 (1.42, 2.83), Hong Kong, 1.61 (1.25, 2.06), and Japan, 1.44 (1.13, 1.85), the estimated relative risks are higher than those of the United States and more highly significant after adjusting for the potential bias.
- Strong associations for highest exposure groups. Examining the groups with the highest exposure levels increases the ability to detect an effect, if it exists. Nine of the sixteen studies worldwide for which there are sufficient exposure-level data are statistically significant for the highest exposure group, despite most having low statistical power. The overall pooled estimate of 1.81 for the highest exposure groups is highly statistically significant (90% C.I. = 1.60, 2.05; $p < 10^{-6}$). For the United States, the overall pooled estimate of 1.38 (seven studies, corrected for smoker misclassification bias) is also highly statistically significant (90% C.I. = 1.13, 1.70; $p = 0.005$).
- Confounding cannot explain the association. The broad-based evidence for an association found by independent investigators across several countries, as well as the positive exposure-response trends observed in most of the studies that analyzed for them, make any single confounder highly unlikely as an explanation for the results. In addition, this report examined potential confounding factors (history of lung disease, home heat sources, diet, occupation) and concluded that none of these factors could account for the observed association between lung cancer and ETS.

1.3.1.2. *Estimation of Population Risk*

The individual risk of lung cancer from exposure to ETS does not have to be very large to translate into a significant health hazard to the U.S. population because of the large number of smokers and the widespread presence of ETS. Current smokers comprise approximately 26% of the U.S. adult population and consume more than one-half trillion cigarettes annually (1.5 packs per day, on average), causing nearly universal exposure to at least some ETS. As a biomarker of tobacco smoke uptake, cotinine, a metabolite of the tobacco-specific compound nicotine, is detectable in the blood, saliva, and urine of persons recently exposed to tobacco smoke. Cotinine has typically been detected in 50% to 75% of reported nonsmokers tested (50% equates to 63 million U.S. nonsmokers age 18 or older).

The best estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers age 35 and over attributable to ETS (Chapter 6) is based on data pooled from all 11 U.S. epidemiologic studies of never-smoking women married to smoking spouses. Use of U.S. studies should increase the confidence in these estimates. Some mathematical modeling is required to adjust for expected bias from misclassification of smoking status and to account for ETS exposure from sources other than spousal smoking. The overall relative risk estimate of 1.19 for the United States, already adjusted for smoker misclassification bias, becomes 1.59 after adjusting for background ETS sources (1.34 for nonspousal exposures only). Assumptions are also needed to relate responses in female never-smokers to those in male never-smokers and ex-smokers of both sexes, and to estimate the proportion of the nonsmoking population exposed to various levels of ETS. Overall, however, the assumptions necessary for estimating risk add far less uncertainty than other EPA quantitative assessments. This is because the extrapolation for ETS is based on a large database of human studies, all at levels actually expected to be encountered by much of the U.S. population.

The components of the 3,000 lung cancer deaths figure include approximately 1,500 female never-smokers, 500 male never-smokers, and 1,000 former smokers of both sexes. More females are estimated to be affected because there are more female than male nonsmokers. These component estimates have varying degrees of confidence; the estimate of 1,500 deaths for female never-smokers has the highest confidence because of the extensive database. The estimate of 500 for male never-smokers is less certain because it is based on the female never-smoker response and is thought to be low because males are generally subject to higher background ETS exposures than females. Adjustment for this higher background exposure would lead to higher risk estimates. The estimate of 1,000 lung cancer deaths for former smokers of both sexes is considered to have the lowest confidence, and the assumptions used are thought to make this estimate low as well.

Workplace ETS levels are generally comparable with home ETS levels, and studies using body cotinine measures as biomarkers demonstrate that nonspousal exposures to ETS are often greater than exposure from spousal smoking. Thus, this report presents an alternative breakdown of the estimated 3,000 ETS-attributable lung cancer deaths between spousal and nonspousal exposures. By extension of the results from spousal smoking studies, coupled with biological measurements of exposure, more lung cancer deaths are estimated to be attributable to ETS from combined nonspousal exposures--2,200 of both sexes--than from spousal exposure--800 of both sexes. This spouse-versus-other-sources partitioning depends on current exposure estimates that may or may not be applicable to the exposure period of interest. Thus, this breakdown contains this element of uncertainty in addition to those discussed above with respect to the previous breakdown.

An alternative analysis, based on the large Fontham et al. (1991) study, which is the only study that provides biomarker estimates of both relative risk and ETS exposure, yields population risk point estimates of 2,700 and 3,600. These population risk estimates are highly consistent with the estimate of 3,000 based on the combined U.S. studies.

While there is statistical variance around all of the parameters used in the quantitative assessment, the two largest areas of uncertainty are probably associated with the relative risk estimate for spousal ETS exposure and the parameter estimate for the background ETS exposure adjustment. A sensitivity analysis that independently varies these two estimates yields population risk estimates as low as 400 and as high as 7,000. These extremes, however, are considered unlikely; the more probable range is narrower, and the generally conservative assumptions employed suggest that the actual population risk number may be greater than 3,000. Overall, considering the multitude, consistency, and quality of all these studies, the weight-of-evidence conclusion that ETS is a known human lung carcinogen, and the limited amount of extrapolation necessary, the confidence in the estimate of approximately 3,000 lung cancer deaths is medium to high.

1.3.2. ETS and Noncancer Respiratory Disorders

Exposure to ETS from parental smoking has been previously linked with increased respiratory disorders in children, particularly in infants. Several studies have confirmed the exposure and uptake of ETS in children by assaying saliva, serum, or urine for cotinine. These cotinine concentrations were highly correlated with smoking (especially by the mother) in the child's presence. Nine to twelve million American children under 5 years of age, or one-half to two-thirds of all children in this age group, may be exposed to cigarette smoke in the home (American Academy of Pediatrics, 1986; Overpeck and Moss, 1991).

With regard to the noncancer respiratory effects of passive smoking, this report focuses on epidemiologic evidence appearing since the two major reports of 1986 (NRC and U.S. DHHS) that bears on the potential association of parental smoking with detrimental respiratory effects in their children. These effects include symptoms of respiratory irritation (cough, sputum production, or wheeze); acute diseases of the lower respiratory tract (pneumonia, bronchitis, and bronchiolitis); acute middle ear infections and indications of chronic middle ear infections (predominantly middle ear effusion); reduced lung function (from forced expiratory volume and flow-rate measurements); incidence and prevalence of asthma and exacerbation of symptoms in asthmatics; and acute upper respiratory tract infections (colds and sore throats). The more than 50 recently published studies reviewed here essentially corroborate the previous conclusions of the 1986 reports of the NRC and Surgeon General regarding respiratory symptoms, respiratory illnesses, and pulmonary function, and they strengthen support for those conclusions by the additional weight of evidence (Chapter 7). For example, new data on middle ear effusion strengthen previous evidence to warrant the stronger conclusion in this report of a causal association with parental smoking. Furthermore, recent studies establish associations between parental smoking and increased incidence of childhood asthma. Additional research also supports the hypotheses that in utero exposure to mother's smoke and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization, changes that are known to predispose children to early respiratory illness. Early respiratory illness can lead to long-term pulmonary effects (reduced lung function and increased risk of chronic obstructive lung disease).

This report also summarizes the evidence for an association between parental smoking and SIDS, which was not addressed in the 1986 reports of the NRC or Surgeon General. SIDS is the most common cause of death in infants ages 1 month to 1 year. The cause (or causes) of SIDS is unknown; however, it is widely believed that some form of respiratory pathogenesis is generally involved. The current evidence strongly suggests that infants whose mothers smoke are at an increased risk of dying of SIDS, independent of other known risk factors for SIDS, including low birthweight and low gestational age, which are specifically associated with active smoking during pregnancy. However, available studies do not allow this report to conclude whether that increased risk is related to in utero versus postnatal exposure to tobacco smoke products, or to both.

The 1986 reports of the NRC and Surgeon General conclude that both the prevalence of respiratory symptoms of irritation and the incidence of lower respiratory tract infections are higher in children of smoking parents. In the 18 studies of respiratory symptoms subsequent to the 2 reports, increased symptoms (cough, phlegm production, and wheezing) were observed in a range of ages from birth to midteens, particularly in infants and preschool children. In addition to the studies on symptoms of respiratory irritation, 10 new studies have addressed the topic of parental smoking and acute lower respiratory tract illness in children, and 9 have reported statistically significant associations. The cumulative evidence is conclusive that parental smoking, especially the mother's, causes an increased incidence of respiratory illnesses from birth up to the first 18 months to 3 years of life, particularly for bronchitis, bronchiolitis, and pneumonia. Overall, the evidence confirms and strengthens the previous conclusions of the NRC and Surgeon General.

Recent studies also solidify the evidence for the conclusion of a causal association between parental smoking and increased middle ear effusion in young children. Middle ear effusion is the most common reason for hospitalization of young children for an operation.

At the time of the Surgeon General's report on passive smoking (U.S. DHHS, 1986), data were sufficient to conclude only that maternal smoking may influence the severity of asthma in children. The recent studies reviewed here strengthen and confirm these exacerbation effects. The new evidence is also conclusive that ETS exposure increases the number of episodes of asthma in children who already have the disease. In addition, the evidence is suggestive that ETS exposure increases the number of new cases of asthma in children who have not previously exhibited symptoms, although the results are statistically significant only with children whose mothers smoke 10 or more cigarettes per day. While the evidence for new cases of asthma itself is not conclusive of a causal association, the consistently strong association of ETS both with increased frequency and severity of the asthmatic symptoms and with the established ETS effects on the immune system and airway hyperresponsiveness lead to the conclusion that ETS is a risk factor for induction of asthma in previously asymptomatic children.

Regarding the effects of passive smoking on lung function in children, the 1986 NRC and Surgeon General reports both conclude that children of parents who smoke have small decreases in tests of pulmonary output function of both the larger and smaller air passages when compared with the children of nonsmokers. As noted in the NRC report, if ETS exposure is the cause of the observed decrease in lung function, the effect could be due to the direct action of agents in ETS or an indirect consequence of increased occurrence of acute respiratory illness related to ETS.

Results from eight studies on ETS and lung function in children that have appeared since those reports add some additional confirmatory evidence suggesting a causal rather than an indirect relationship. For the population as a whole, the reductions are small relative to the interindividual variability of each lung function parameter. However, groups of particularly susceptible or heavily exposed children have shown larger decrements. The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. Exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

With respect to lung function effects in adults exposed to ETS, the 1986 NRC and Surgeon General reports found the data at that time inconclusive, due to high interindividual variability and the existence of a large number of other risk factors, but compatible with subtle deficits in lung function. Recent studies confirm the association of passive smoking with small reductions in lung function. Furthermore, new evidence also has emerged suggesting a subtle association between exposure to ETS and increased respiratory symptoms in adults.

Some evidence suggests that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

In reviewing the available evidence indicating an association (or lack thereof) between ETS exposure and the different noncancer respiratory disorders analyzed in this report, the possible role of several potential confounding factors was considered. These include other indoor air pollutants; socioeconomic status; effect of parental symptoms; and characteristics of the exposed child, such as low birthweight or active smoking. No single or combined confounding factors can explain the observed respiratory effects of passive smoking in children.

For diseases for which ETS has been either causally associated (LRIs) or indicated as a risk factor (asthma cases in previously asymptomatic children), estimates of population-attributable risk can be calculated. A population risk assessment (Chapter 8) provides a probable range of estimates that 8,000 to 26,000 cases of childhood asthma per year are attributable to ETS exposure from mothers who smoke 10 or more cigarettes per day. The confidence in this range of estimates is medium and is dependent on the suggestive evidence of the database. While the data show an effect only for children of these heavily smoking mothers, additional cases due to lesser ETS exposure also are a possibility. If the effect of this lesser exposure is considered, the range of estimates of new cases presented above increases to 13,000 to 60,000. Furthermore, this report estimates that the additional public health impact of ETS on asthmatic children includes more than 200,000 children whose symptoms are significantly aggravated and as many as 1,000,000 children who are affected to some degree.

This report estimates that ETS exposure contributes 150,000 to 300,000 cases annually of lower respiratory tract illness in infants and children younger than 18 months of age and that 7,500 to 15,000 of these will require hospitalization. The strong evidence linking ETS exposure to increased incidence of bronchitis, bronchiolitis, and pneumonia in young children gives these estimates a high degree of confidence. There is also evidence suggesting a smaller ETS effect on children between the ages of 18 months and 3 years, but no additional estimates have been computed for this age group. Whether or not these illnesses result in death has not been addressed here.

In the United States, more than 5,000 infants die of SIDS annually. It is the major cause of death in infants between the ages of 1 month and 1 year, and the linkage with maternal smoking is well established. The Surgeon General and the World Health Organization estimate that more than 700 U.S. infant deaths per year from SIDS are attributable to maternal smoking (CDC, 1991a, 1992b). However, this report concludes that at present there is not enough direct evidence supporting the contribution of ETS exposure to declare it a risk factor or to estimate its population impact on SIDS.

3. ESTIMATION OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE

3.1. INTRODUCTION

Environmental tobacco smoke (ETS) is composed of exhaled mainstream smoke (MS) from the smoker, sidestream smoke (SS) emitted from the smoldering tobacco between puffs, contaminants emitted into the air during the puff, and contaminants that diffuse through the cigarette paper and mouth end between puffs (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). These emissions contain both vapor phase and particulate contaminants. SS is the major component of ETS, contributing nearly all of the vapor phase constituents and over half of the particulate matter.

Overall, ETS is a complex mix of over 4,000 compounds. This mix contains many known or suspected human carcinogens and toxic agents. The information necessary to evaluate human exposures to each of the compounds of human health interest in ETS does not exist.

Recognizing that it is impractical to characterize the many individual compounds that make up ETS and to then assess exposures to those compounds, this chapter focuses on the characterization of the complex ETS contaminant mix and exposure to it by nonsmokers. Available data on the physical and chemical properties of sidestream and mainstream smoke are compared to assess the potential for the release of known or suspected human carcinogens and toxic agents into indoor environments where human exposures occur. The available published data are reviewed to determine whether ETS constituents exist in elevated levels in various indoor environments where smoking occurs and whether human exposures ensue. Particular attention is focused upon environmental and biological marker compounds that serve as proxies for the complex ETS mix and the compounds of human health interest.

The available biomarker data for ETS clearly show that levels of ETS contaminants encountered indoors by nonsmokers are of sufficient magnitude to be absorbed and to result in measurable doses. Chapters 6 and 8 and Appendix B use such biomarker data for estimating relative residential and nonresidential ETS exposures in calculating the associated risks for lung cancer and various noncancer respiratory effects.

Epidemiologic studies relating exposure to ETS with lung cancer (Chapter 5) and respiratory disorders other than cancer (Chapter 7) frequently rely on questionnaires to assess level of exposure. This chapter reviews the limited number of studies that have attempted to validate questionnaires with objective measures of exposure. All of these are population surveys and not epidemiologic disease studies. The few studies that compare body cotinine levels with childhood respiratory disease occurrences are discussed in Chapters 7 and 8.

This chapter concludes that (1) MS, SS, and ETS are chemically similar and contain a number of known or suspected human carcinogens and toxic compounds; (2) marker compounds for ETS are measurable in a variety of indoor environments; (3) exposure to ETS is extensive; and (4) there is a measurable uptake of ETS by nonsmokers.

3.2. PHYSICAL AND CHEMICAL PROPERTIES

Over the past several years, there have been a number of reviews of the physical and chemical properties of mainstream and sidestream cigarette smoke (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). A particularly detailed review is contained in the recent book by Guerin et al. (1992). This section summarizes the findings of these reviews to identify the similarities and differences in mainstream and sidestream emissions and to establish that known and suspected human carcinogens and toxic agents are released into occupied spaces from tobacco combustion. Data contained in these reviews, as well as recently published material, are also presented to document that sidestream emissions of notable air contaminants result in measurable increases of these contaminants in indoor locations where individuals spend time.

The physical and chemical characterization of MS air contaminant emissions from cigarettes, cigars, or pipes is derived from laboratory-based studies that have typically utilized standardized testing protocols (FTC, 1990; Guerin et al., 1992). The data available are primarily for tobacco combustion in cigarettes and provide a substantial database on the nature of MS. These protocols employ smoking machines, set puff volumes and frequencies, and standardized air contaminant collection protocols (small chambers, Cambridge filters, chamber air flow rates, etc.). Existing standardized protocols reflect conditions representative of human smoking practices of over 30 years ago for nonfiltered cigarettes and may not reflect current human smoking parameters for today's filtered low-tar cigarettes (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). It has been suggested that current standardized protocols, particularly for filter cigarettes, may underestimate MS deliveries (Guerin et al., 1992). MS air contaminant emission rates determined in these studies using standardized protocols can be affected by a number of factors, such as puff volume, air dilution rate, paper porosity, filter ventilation air flow around the cigarette, and moisture content of the tobacco. Actual smoking habits of individuals can also dramatically alter the MS deliveries. Variability in any of the factors can affect the nature and quantity of the MS emissions.

Standardized testing protocols for assessing the physical and chemical nature of SS emissions from cigarette smoke do not exist, and data on SS are not as extensive as those for MS emissions. Protocols used for the generation and collection of SS emissions typically use standardized MS protocols (smoking machines, puff volumes, etc.) with modifications in the test devices (use of small chambers) that allow for the simultaneous collection of SS emissions for analysis (Dube and Green, 1982; McRae, 1990; Rickert et al., 1984).

The protocols for the collection of SS emissions are such that results can be directly compared to MS emissions and thus provide valuable insights into the physical and chemical nature of ETS. It should be noted, however, that the SS emissions collected under these protocols may be somewhat different from ETS emissions. ETS also contains exhaled MS, which has not yet been characterized. Exhaled MS can contribute from 15% to 43% of the particulate matter in ETS, though little of the gas phase contaminants (Baker and Proctor, 1990). In addition, SS samples are not collected under conditions where the emissions are diluted and "aged," as is ETS. The aging and dilution of the SS emissions can produce changes in phase distribution of the contaminants.

Results of laboratory evaluations have indicated substantial similarities and some differences between MS and SS emissions from cigarettes (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992). Differences in SS and MS emissions are due to differences in the temperature of combustion of the tobacco, Ph, and degree of dilution with air, which is accompanied by a corresponding rapid decrease in temperature. SS is generated at a lower temperature (approximately 600°C between puffs vs. 800-900°C for MS during puffs) and at a higher Ph (6.7-7.5 vs. 6.0-6.7) than MS. Being slightly more alkaline, SS contains more ammonia, is depleted of acids, contains greater quantities of organic bases, and contains less hydrogen cyanide than MS. Differences in MS and SS are also ascribable to differences in the oxygen concentration (16% in MS vs. 2% in SS). SS contaminants are generated in a more reducing environment than those in MS, which will affect the distribution of some compounds--nitrosamines, for example, are present in greater concentrations in SS than in MS.

SS is rapidly diluted in air, which results in a SS particle size distribution smaller than that for MS and in the potential for changes in phase distribution for several constituents. Nicotine, for example, while predominantly in the particle phase in MS, is found predominantly in the gas phase in ETS (Eudy et al., 1985). The shift to gas phase is due to the rapid dilution in SS. SS particle size is typically in the range of 0.01-1.0 μm, while MS particle size is 0.1-1.0 μm. The SS size distribution shifts to small sizes with increasing dilution (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Ingebrethsen and Sears, 1985). The differences in size distribution for MS and SS particles, as well as the different breathing patterns of smokers and nonsmokers, have implications for deposition of the produced particle contaminants in various regions of the respiratory tract. Estimates of from 47% to more than 90% deposition for MS and of 10% deposition for SS have been reported (U.S. DHHS, 1986).

Despite quantitative differences and potential differences in phase distributions, the air contaminants emitted in MS and SS are qualitatively very similar in their chemical composition because they are produced by the same process. Over 4,000 compounds have been identified in laboratory-based studies of MS (Dube and Green, 1982; Roberts, 1988). In a 1986 IARC monograph evaluating the carcinogenic risk of tobacco smoke to humans (IARC, 1986), 42 individual MS components were identified as carcinogenic in bioassays with laboratory animals, with many of these either known or suspected human carcinogens. Many additional compounds in MS have been identified as toxic compounds. Although SS emissions have not been chemically characterized as completely as MS emissions, many of the compounds found in MS emissions, including a host of carcinogenic agents, are found in SS emissions (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Dube and Green, 1982; Roberts, 1988) and at emission rates considerably higher than for MS.

Part of the data available from studies of MS and SS emissions is shown in Table 3-1 (extracted from NRC, 1986). These data are for nonfilter cigarettes and represent a summary of data from several sources. It is immediately obvious from Table 3-1 that SS and MS contain many of the same notable air contaminants, including several known or suspected human toxic and carcinogenic agents, and that SS emissions are often considerably higher than MS emissions. For the compounds shown in Table 3-1, all of the five known human carcinogens, nine probable human carcinogens, and three animal carcinogens are emitted at higher levels in SS than in MS, several by an order of magnitude or more. For example, *N*-nitrosodimethylamine, a potent animal carcinogen, is emitted in quantities 20 to 100 times higher in SS than in MS. Table 3-1 similarly shows that several toxic compounds found in MS are also found in SS (carbon monoxide, ammonia, nitrogen oxides, nicotine, acrolein, acetone, etc.). Again, for many of these compounds, SS emissions are higher than MS emissions--in some cases by an order of magnitude or higher.

The SS/MS emission ratios shown in Table 3-1 can be highly variable and potentially misleading because, as noted earlier, a number of factors can have a substantial impact on MS emissions. A filtered cigarette, for example, can substantially reduce MS of total mass well below that shown in Table 3-1, thus resulting in a much higher SS/MS ratio. A number of recent studies (Adams et al., 1987; Guerin, 1987; Higgins et al., 1987; Chortyk and Schlotzhauer, 1989; Browne et al., 1980; Guerin et al., 1992) indicate that, quantitatively, SS emissions show little variability as a function of a number of variables (puff volume, filter vs. nonfilter cigarette, and filter ventilation). The lack of substantial variability in SS emissions is related to the fact that sidestream emissions are primarily related to the weight of tobacco and paper consumed during

Table 3-1. Distribution of constituents in fresh, undiluted mainstream smoke and diluted sidestream smoke from nonfilter cigarettes[1]

Constituent	Amount in MS	Range in SS/MS
Vapor phase:[2]		
Carbon monoxide	10-23 mg	2.5-4.7
Carbon dioxide	20-40 mg	8-11
Carbonyl sulfide	12-42 μg	0.03-0.13
Benzene[3]	12-48 μg	5-10
Toluene	100-200 μg	5.6-8.3
Formaldehyde[4]	70-100 μg	0.1-~50
Acrolein	60-100 μg	8-15
Acetone	100-250 μg	2-5
Pyridine	16-40 μg	6.5-20
3-Methylpyridine	12-36 μg	3-13
3-Vinylpyridine	11-30 μg	20-40
Hydrogen cyanide	400-500 μg	0.1-0.25
Hydrazine[4]	32 ng	3
Ammonia	50-130 μg	3.7-5.1
Methylamine	11.5-28.7 μg	4.2-6.4
Dimethylamine	7.8-10 μg	3.7-5.1
Nitrogen oxides	100-600 μg	4-10
N-Nitrosodimethylamine[4]	10-40 ng	20-100
N-Nitrosodiethylamine[4]	ND-25 ng	<40
N-Nitrosopyrrolidine[4]	6-30 ng	6-30
Formic acid	210-490 μg	1.4-1.6
Acetic acid	330-810 μg	1.9-3.6
MethCyl chloride	150-600 μg	1.7-3.3
1,3-Butadiene[4,6]	69.2 μg	3-6

(continued on the following page)

Table 3-1. (continued)

Constituent	Amount in MS	Range in SS/MS
Particulate phase:[2]		
Particulate matter[7]	15-40 mg	1.3-1.9
Nicotine	1-2.5 mg	2.6-3.3
Anatabine	2-20 μg	<0.1-0.5
Phenol	60-140 μg	1.6-3.0
Catechol	100-360 μg	0.6-0.9
Hydroquinone	110-300 μg	0.7-0.9
Aniline[4]	360 ng	30
2-Toluidine	160 ng	19
2-Naphthylamine[3]	1.7 ng	30
4-Aminobiphenyl[3]	4.6 ng	31
Benz[a]anthracene[5]	20-70 ng	2-4
Benzo[a]pyrene[4]	20-40 ng	2.5-3.5
Cholesterol	22 μg	0.9
γ-Butyrolactone[5]	10-22 μg	3.6-5.0
Quinoline	0.5-2 μg	3-11
Harman[8]	1.7-3.1 μg	0.7-1.7
N-Nitrosonornicotine[5]	200-3,000 ng	0.5-3
NNK[9]	100-1,000 ng	1-4
N-Nitrosodiethanolamine[4]	20-70 ng	1.2
Cadmium[4]	110 ng	7.2
Nickel[3]	20-80 ng	13-30
Zinc	60 ng	6.7
Polonium-210[3]	0.04-0.1 pCi	1.0-4.0
Benzoic acid	14-28 μg	0.67-0.95
Lactic acid	63-174 μg	0.5-0.7
Glycolic acid	37-126 μg	0.6-0.95
Succinic acid	110-140 μg	0.43-0.62
PCDDs and PCDFs[10]	1 pg	2

(continued on the following page)

Table 3-1. (continued)

[1] Data in this table come from the NRC report (1986), except where noted, which compiled data from Elliot and Rowe, 1975; Schmeltz et al., 1979; Hoffman et al., 1983; Klus and Kuhn, 1982; Sakuma et al., 1983, 1984a, 1984b; and Hiller et al., 1982. Full references are given in NRC, 1986. Diluted SS is collected with airflow of 25 mL/s, which is passed over the burning cone; as presented in the NRC report on passive smoking (1986).
[2] Separation into vapor and particulate phases reflects conditions prevailing in MS and does not necessarily imply same separation in SS.
[3] Known human carcinogen, according to U.S. EPA or IARC.
[4] Probable human carcinogen, according to U.S. EPA or IARC.
[5] Animal carcinogen (Vainio et al., 1985).
[6] Data from Brunnemann et al., 1990.
PCDDs = polychlorinated dibenzo-p-dioxins;
PCDFs = polychlorinated dibenzofurans.
[7] Contains di- and polycyclic aromatic hydrocarbons, some of which are known animal carcinogens.
[8] 1-methyl-9*H*-pyrido[3,4-*b*]-indole.
[9] NNK = 4-(*N*-methyl-*N*-nitrosamino)-1-(3-pyridyl)-1-butanone.
[10] Data from Löfroth and Zebühr, 1992. Amount is given as International Toxic Equivalent Factor (I-TEF).

the smoldering period, with little influence exerted by cigarette design (Guerin et al., 1992). More recent summary data on SS emission rates from filtered test cigarettes and commercial cigarettes for many compounds of human health interest are presented by Guerin et al. (1992) and shown, with modifications, in Table 3-2. Much of the data in Table 3-2 is extracted from detailed data presented in an R.J. Reynolds (1988) report. Table 3-2, like Table 3-1, documents that appreciable quantities of important air contaminants are emitted into the air from SS emissions resulting from tobacco combustion. The table demonstrates that SS emissions are reasonably similar across different brands of cigarettes, varying by only a factor of 2-3. So, while MS emissions can vary considerably (Table 3-1), SS emissions are relatively constant (Table 3-2).

In summary, the available data indicate that tobacco combustion results in the emission of a large number of known toxic compounds and that many of these will be released at rates that are higher in SS than in MS. Emphasis in characterizing SS emissions has been placed upon those carcinogens and toxic compounds found in MS. Although not all of the SS emissions have been characterized, the available data showing SS to be enriched in many of the same carcinogens and toxic agents found in MS lead to the conclusion that ETS will contain the same hazardous compounds. This conclusion provides the basis for the toxicological comparison of these complex mixtures in Chapter 4. The enrichment of several known or suspected carcinogens in SS relative to MS suggests that the SS contaminant mix may be even more carcinogenic than the MS mix, per

Table 3-2. Example sidestream cigarette smoke deliveries[1]

Constituent	Kentucky reference[2]	Commercial
	Milligrams per cigarette	
Condensate		36-67
Total particulate matter	16.9	16-36, 20-23
Nicotine	5.6	5.7-11.2, 2.7-6.1
Carbon monoxide	54	41-67
Carbon dioxide	474	
Nitrogen oxides	0.9	
Ammonia	9.1	
Formaldehyde	0.7	
Acetaldehyde	4.2	
Acrolein	1.3, 1.4	0.7-1.0
Propionaldehyde	0.9	
Benzene	0.3, 0.4, 0.7	0.3-0.5
Toluene	0.8, 1.3	0.8-1.1
Styrene		
Pyrrole	0.4	
Pyridine	0.3	
3-Vinylpyridine		
3-Hydroxypyridine		
Limonene	0.3	<0.1-0.4
Neophytadiene		0.1-0.2
Isoprene	2.5, 6.1	4.4-6.5
nC_{27}-nC_{33}	0.2-0.8	
Acetonitrile	1.0, 0.8[3]	
Acrylonitrile	0.2	

(continued on the following page)

Table 3-2. (continued)

Constituent	Kentucky reference[2]	Commercial
	Micrograms per cigarette	
Hydrogen cyanide	53, 17[3]	
Phenol		44-371
o-Cresol		24-98
m + p-Cresol		59-299
Catechol		46-189
Hydroquinone		26-256
Naphthalene		53-177
Phenanthrene		2.4
Anthracene		0.7
Fluoranthene		0.7
Pyrene		0.5
Benz[a]anthracene	0.2	0.2
Benzo[a]pyrene	0.1	0.1
NNN[4]	0.2	1.7
NNK[4]	0.4	0.4
NAT[4]	0.1	
NAB[4]	<0.1	
DMNA[4]	0.3	0.7-1.0
EMNA[4]		<0.1
DENA[4]		<0.1-0.1
NPYR[4]	0.2	0.2-0.4
2-Naphthylamine		<0.1-1[5]
4-Aminobiphenyl		<0.1-0.2[5]
Nickel		
Cadmium		
Lead		
Chromium		

(continued on the following page)

Table 3-2. (continued)

[1] Table reprinted from Guerin et al. 1992, who compiled data from Browne et al., 1990; Brunnemann et al., 1977, 1978, and 1990; Chortyk and Schlotzhauer, 1989; Grimmer et al., 1987; Guerin, 1991; Higgins et al., 1987; Johnson et al., 1973; O'Neill et al., 1987; R.J. Reynolds, 1988; Rickert et al., 1984; Sakuma et al., 1983, 1984a, 1984b; and Norman et al., 1983. Full references are given in Guerin et al., 1992.

[2] Filter 1R4F unless otherwise specified.

[3] Nonfilter 1R1.

[4] *N*-nitrosonornicotine (NNN), 4-methylnitrosoamino-1-(3-pyridinyl)-1-butanone (NNK), *N*-nitrosoanatabine (NAT), *N*-nitrosoanabasine (NAB), dimethylnitrosamine (DMNA), ethylmethylnitrosamine (EMNA), diethylnitrosamine (DENA), *N*-nitrosopyrrolidine (NPYR).

[5] Calculated from NRC, 1986, SS/MS ratio.

unit tobacco burned. The mouse skin painting bioassays of organic extracts of MS and SS reviewed in Chapter 4 add support to the suggestion that SS is a more potent carcinogen than MS. Furthermore, the incomplete chemical characterization of SS emissions means that there may be additional, as yet unidentified compounds in SS of human health interest.

Detailed chemical characterizations of ETS emissions under conditions more typical of actual smoking conditions (e.g., using smokers rather than smoking machines) are limited. As a result, the impact on ETS of factors such as the rapid dilution of SS emissions, adsorption and remission of contaminants, and exhaled MS is not well understood. Several studies conducted in chambers or controlled environments and using smokers (e.g., Benner et al., 1989; Duc and Huynh, 1989; Leaderer and Hammond, 1991; R.J. Reynolds, 1988; NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992) have characterized some of the ETS components (total mass, carbon monoxide, nicotine and other selected compounds, including known carcinogenic and toxic substances). These studies indicate that many of the contaminants of interest in SS are measurable in ETS (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992) and that several SS contaminants (e.g., total mass, carbon monoxide, nicotine) are easily measurable in ETS. It is not known how the MS and SS air contaminant emission data for specific compounds, generated by the standardized testing protocols utilized, compare to data gathered under conditions more representative of actual smoking in occupied spaces.

3.3. ASSESSING ETS EXPOSURE

In the course of a typical day, an individual spends varying amounts of time in a variety of environments (residences, industrial and nonindustrial workplaces, automobiles, public access buildings, outdoors, etc.). While in these different environments, individuals are exposed to a broad and complex spectrum of organic and inorganic chemicals in gaseous and particle forms, as well as a range of viable particles.

ETS is a major source of indoor air contamination because of the large, though decreasing, number of smokers in the population and the quantity and quality of the contaminants emitted into the environment from tobacco combustion (NRC, 1981, 1986). In a 1990 self-reported smoking survey of a representative sample of the U.S. civilian, noninstitutionalized population, it was reported that 50.1% (89.9 million) of the adult population were ever-smokers and 25.5% were current smokers (CDC, 1992). The reported average number of cigarettes smoked per day was 19.1, with 22.9% of smokers reporting smoking 25 or more cigarettes per day. From 1965 through 1985, the overall smoking prevalence among U.S. adults declined 0.5% annually, with a 1.1% annual decline between 1987 and 1990.

In another recent survey (CDC, 1991b), 40.3% (46 million) of employed adults ($\geq$ 18 years old) in 1988 (who reported that their workplace was not in their home) worked in locations where smoking was allowed in designated or other areas. Of the nonsmokers (79.2 million), 36.5% (28.5 million) worked at places that permitted smoking in designated (if any) and other areas. Of these nonsmokers, 59.2% (16.9 million) reported that exposure to ETS in their workplace caused them discomfort. The survey highlighted the importance of the workplace as a major source of ETS exposure in addition to the home.

The available data on ETS exposure to children in the home are limited. However, based on the 1988 National Health Interview Survey on Child Health, 42% of children 5 years of age and under are estimated to live in households with current smokers (Overpeck and Moss, 1991). The home environment is clearly an important source of ETS exposure for children.

Nationally based survey data needed to make direct estimates of the frequency, magnitude, and duration of ETS exposure for nonsmoking adults and children and the different indoor environments in which those exposures occur are not available. The survey data available, however, do indicate that due to the ubiquitous nature of ETS in indoor environments, some unintentional inhalation of ETS by nonsmokers is unavoidable.

The combustion of tobacco results in the emission of a particularly complex array of air contaminants into indoor microenvironments. Data on the chemical composition of mainstream and sidestream cigarette emissions as well as measurements in indoor spaces where smoking occurs indicate that exposure to ETS will result in exposure to toxic and carcinogenic agents (Section 3.2). The nature of the ETS contaminant mix and eventual human exposure is the product of the interaction of several interrelated factors associated with the source, transport, chemical transformation, dispersal, removal, and remission from surfaces, as well as human activities. Efforts to determine adverse health effects of ETS must address the issue of exposure to a complex mixture, which can occur in a number of environments. Assessing exposure to ETS, as with any complex air contaminant mix, is inherently complicated in epidemiologic studies (Leaderer et al., 1992).

Because of the many potentially toxic agents in ETS and the various possible toxicological endpoints of interest, it is neither feasible nor desirable to focus on any one contaminant. Rather, the focus is on gathering information on marker or proxy compounds or other indicators of ETS exposure. In assessing these exposures, both direct and indirect methods can be employed. Direct methods include personal monitoring and measurement of biological markers. Indirect methods employ models to estimate exposures. The modeling approach generally makes use of stationary monitoring and questionnaire data.

Stationary monitoring is used to measure concentrations of air contaminants in different environments. These measured concentrations are then combined with time-activity patterns (time budgets) to determine the average exposure of an individual as the sum of the concentrations in each environment weighed by the time spent in that environment. Monitoring of contaminants might also be supplemented with the monitoring of factors in the environment that affect the contaminant levels measured (meteorological variables, primary compounds, ventilation, etc.). Measurement of these factors, in a carefully chosen set of conditions, can lead to models that predict concentrations in the absence of measured concentrations and provide a means of assessing the impact of efforts to reduce or eliminate exposures. Questionnaires are used to determine time-activity patterns of individuals, to provide a simple categorization of potential exposure, and to obtain information on the properties of the environment affecting the measured levels (number of smokers, amounts smoked, etc.).

ETS exposure measurements, whether conducted to support epidemiological studies or to determine the extent of exposure in nonsmoking individuals, have typically employed air monitoring of indoor spaces, personal monitoring, and questionnaires. Modeling of ETS exposures, while useful in estimating, from measured data, the level of exposure in a variety of indoor spaces under varying conditions, is beyond the scope of this report.

3.3.1. Environmental Concentrations of ETS

The SS emission data discussed in Section 3.2 and shown in Tables 3-1 and 3-2 clearly indicate that tobacco combustion will result in the release of thousands of air contaminants into the environments in which smoking occurs. The concentrations of the known and unidentified contaminants in the ETS complex mix in an enclosed space can exhibit a pronounced spatial and temporal distribution. The concentration is the result of a complex interaction of several important variables, including (1) the generation rate of the contaminant(s) from the tobacco (including both SS and exhaled MS emissions), (2) location in the space that smoking occurs, (3) the rate of tobacco consumption, (4) the ventilation or infiltration rate, (5) the concentration of the contaminant(s) in the ventilation or infiltration air, (6) air mixing in the space, (7) removal of contaminants by surfaces or chemical reactions, (8) re-emission of contaminants by surfaces, and (9) the effectiveness of any air cleaners that may be present. Additional considerations relate to the location at which contaminant measurements are made, the time of sample collection, the duration of sampling, and method of sampling.

Variations in any one of the above factors related to introduction, dispersal, and removal of ETS contaminants can have a marked impact on the resultant indoor ETS constituent concentrations. Any one of these parameters can vary by an order of magnitude or more. For example, infiltration rates in residences can range from 0.1 to over 2.0 air changes per hour, and house volumes can range from 100 to over 700 m^3 (Grimsrud et al., 1982; Grot and Clark, 1979; Billick et al., 1988; Koutrakis et al., 1992). Smoking rates and mixing within and between rooms can also show considerable variability. The potential impact on indoor ETS-related respirable suspended particle (RSP) mass concentrations due to variations in these parameters is demonstrated in Figures 3-1 and 3-2 (these figures were taken directly from Figures 5-4 and 5-5 in NRC, 1986). Figures 3-1 and 3-2 are based on the mass balance model for ETS (NRC, 1986) for a typical range of input parameters encountered in indoor spaces. These figures demonstrate that ETS-generated RSP concentrations in indoor environments can range from less than 20 $\mu g/m^3$ to over 1 mg/m^3 depending upon the location and conditions of smoking.

Numerous field studies in "natural" environments have been conducted to assess the contribution of smoking occupancy to indoor air quality. These studies, summarized in a number of reviews (e.g., NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992), have measured several ETS-related contaminants of human health concern (e.g., particle mass, carbon monoxide, benzene, nicotine, polycyclic aromatic hydrocarbons, *N*-nitrosamines), in a number of enclosed environments (e.g., residential, office, transportation) and under a variety of smoking and ventilation rates. These studies demonstrate that (1) many of the contaminants of health interest found in SS are also found in ETS; (2) ETS contaminants are found above background level in a wide range of indoor environments in which smoking occurs; and (3) the concentrations of ETS contaminants indoors can be highly variable. These findings can be demonstrated for selected ETS-related compounds presented in Figure 3-3 and in Table 3-3.

Figure 3-3 principally utilizes data summaries presented in reviews of indoor measurements of ETS-related compounds in a variety of indoor spaces (NRC, 1986; U.S. DHHS, 1986; and particularly Guerin et al., 1992). Only the range of average concentrations measured in

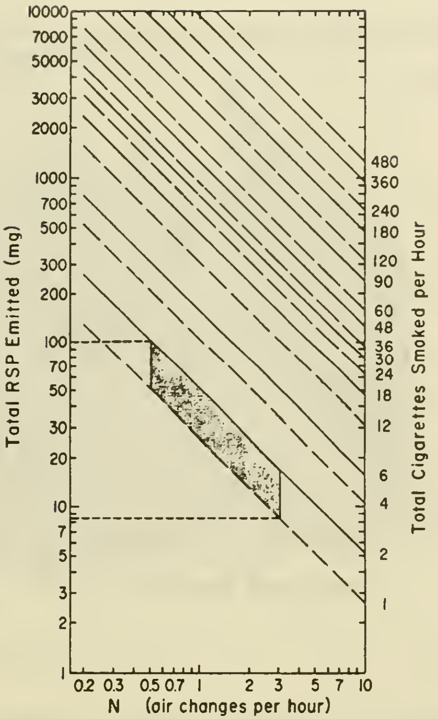


Figure 3-1. Diagram for calculating the respirable suspended particle mass (RSP) from ETS emitted into any occupied space as a function of the smoking rate and removal rate (N). The removal rate is equal to the sum of the ventilation or infiltration rate (n_v) and the removal rate by surfaces (n_s) times the mixing factor. The calculated ETS-related RSP mass determined from this figure serves as an input to Figure 3-2 to determine the ETS-related RSP mass concentration in any space in $\mu g/m^3$. Smoking rates (diagonal lines) are given as cigarettes smoked per hour. Mixing is determined as a fraction, and n_v and n_s are in air changes per hour (ach). All three parameters have to be estimated or measured. Calculations were made using the equilibrium form of the mass-balance equation and assume a fixed emission rate of 26 mg/m^3 of RSP.

Shaded area shows the range of RSP emissions that could be expected for a residence with one smoker smoking at a rate of either 1 or 2 cigarettes per hour for the range of mixing, ventilation, and removal rates occurring in residences under steady-state conditions.

Source: NRC, 1986.

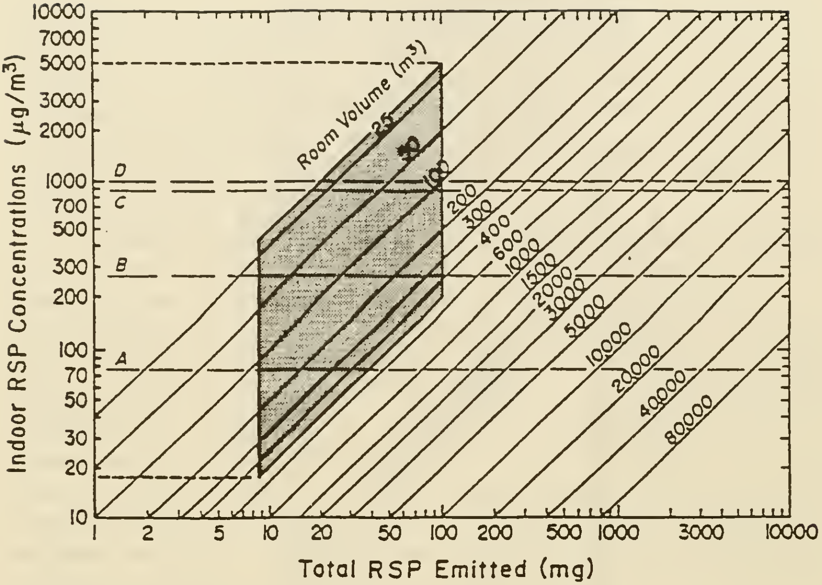
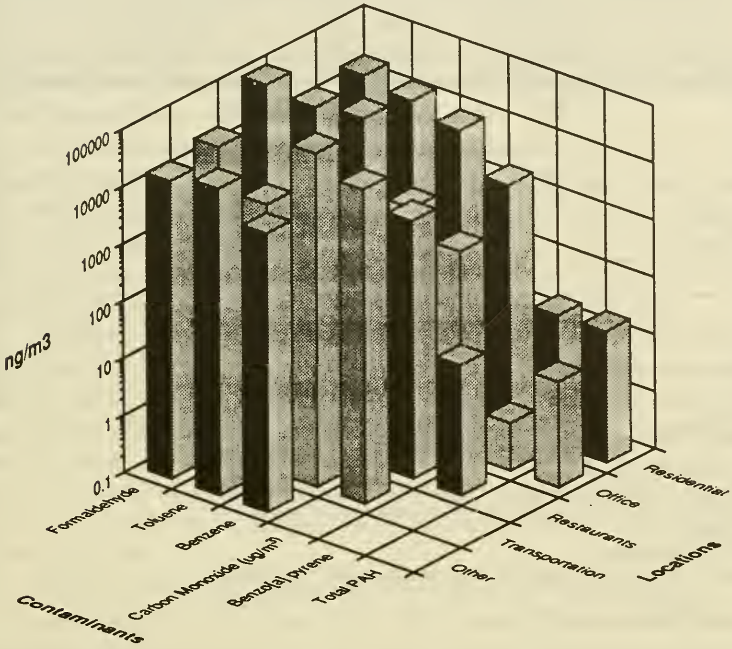


Figure 3-2. Diagram to calculate the ETS-associated respirable suspended particle mass (RSP) concentration in μg/m³ in a space as a function of total mass of ETS-generated RSP emitted in mg (determined from Figure 3-1) and the volume of a space (diagonal lines). The concentrations shown assume a background level of zero in the space. The particle concentrations shown are estimates during smoking occupancy. The dashed horizontal lines (A, B, C, and D) refer to National Ambient Air Quality Standards (health-related) for total suspended particulates established by the U.S. Environmental Protection Agency. A is the annual geometric mean. B is the 24-hour value not to be exceeded more than once a year. C is the 24-hour air pollution emergency level. D is the 24-hour significant harm level. Shaded area shows the range of concentrations expected (from Figure 3-1) for a range of typical volumes of U.S. residences and rooms in these residences.

Source: NRC, 1986.



Range of Average Indoor Concentrations of Noteable ETS Contaminants Associated with Smoking Occupancy

Figure 3-3. Range of average indoor concentrations for notable ETS contaminants associated with smoking occupancy for different indoor environments. Ranges of averages are principally from tables presented in Guerin et al. (1992), although other sources were used (NRC, 1986; U.S. DHHS, 1986; Turk et al., 1987). Background levels are subtracted. Maximum recorded values are typically orders of magnitude higher than averages shown.

Table 3-3. Tobacco-specific *N*-nitrosamines in indoor air (ng/m^3)[1]

Site	Approx. # of cigarettes smoked	Collection time (hours)	Flow rate (liters/ min.)	Tobacco-specific *N*-nitrosamines NNN[2]	NAT[2]	NNK[2]
Bar I	25-35	3	3.2	22.8	9.2	23.8
Bar II	10-15	3	3.2	8.3	6.2	9.6
Bar III	10-15	3	3.2	4.3	3.7	11.3
Restaurant[3]	25-30	6	2.15	1.8	1.5	1.4
Restaurant[3]	40-50	8	2.1	ND	ND	3.3
Car[4]	13	3.3	2.15	5.7	9.5	29.3
Train I	50-60	5.5	3.3	ND	ND	4.9
Train II	50-60	6	3.3	ND	ND	5.2
Office	25	6.5	3.3	ND	ND	26.1
Smoker's Home	30	3.5	3.3	ND	ND	1.9

[1] Data corrected for recovery.
[2] NNN = NNN-*N*-nitrosonornicotine; NAT = NAT-*N*-nitrosoanataline;
NNK = NNK-4-methyllnitrosoamino-1-(3 pyridinyl)-1-butanone.
[3] Smoking section.
[4] Windows partially open.
ND = not detected (in some cases due to chromatographic interference).

Source: Brunnemann et al., 1992.

different environments is shown. Maximum values, which can range up to two or more orders of magnitude above the averages, are not shown in Figure 3-3. Background levels for nonsmoking conditions have been subtracted. When smoking occurs, concentrations of total polycyclic aromatic hydrocarbons, benzo[a]pyrene, benzene, formaldehyde, toluene, and carbon monoxide will be elevated above background levels in a variety of indoor environments. Figures 3-7 and 3-8 present a similar summary with the same conclusions for two other ETS-related contaminants--respirable suspended particle mass and nicotine.

N-nitrosamines are important constituents of SS because they are considered to be carcinogenic, because they are emitted in much larger quantities in SS than in MS (Table 3-1), and because tobacco combustion is the only identified air source in the nonoccupational indoor environment. Guerin et al. (1992) reviewed the available data on indoor levels of *N*-nitrosamines related to smoking occupancy. They concluded that levels associated with smoking can range from less than detectable to as high as 100 ng/m^3 for nitrosodimethylamine (NDMA) under conditions of heavy smoking. A more typical range of concentrations of NDMA were < 10-40 ng/m^3. In a recent paper, Brunnemann et al. (1992) demonstrated that exposure to tobacco specific *N*-nitrosamines can occur in a variety of indoor spaces under a range of smoking conditions (Table 3-3).

The potential for high exposures of nonsmokers to carcinogenic components found enriched in SS can be demonstrated in the case of 4-aminobiphenyl (4-ABP). Tables 3-1 and 3-2 show 4-ABP emissions in SS to be approximately 30 times higher than in MS (100-200 μg/cig). Despite the fact that SS emissions of 4-ABP are diluted rapidly in the indoor environment, presumably resulting in considerably less exposure than to smokers, 4-ABP Hb adduct levels in nonsmokers have been found to be 10% to 20% of those in smokers (see Section 3.3.2).

There are important circumstances where concentrations of ETS-related contaminants in indoor spaces may considerably underestimate potential levels of exposure. These circumstances occur when the SS emissions or exhaled MS emissions are in direct proximity to a nonsmoker (e.g., an infant held by a smoking mother or father, or when a nonsmoker is directly downwind of the plume of a smoldering cigarette). While there are no measurements to assess the impact on the nonsmoker's exposure under these conditions, it is an important exposure and will be much higher than would be predicted from existing environmental measurements of more diluted SS and exhaled MS emissions.

The data discussed above represent concentrations measured in selected indoor environments and indicate that exposure will occur for individuals in those spaces. Estimating the actual level of exposure (concentration × time) requires knowledge of the actual time spent in those environments.

3.3.1.1. *Markers for Environmental Tobacco Smoke*

Although ETS is a major source of indoor air contaminants, the actual contribution of ETS to indoor air is difficult to assess due to the background levels of many contaminants contributed from a variety of other indoor and outdoor sources. Relatively few of the individual constituents of the ETS mix have been identified and characterized. In addition, little is known about the role of individual ETS constituents in eliciting the adverse health and nuisance effects observed. However, the issue is not how to fully characterize the exposure to each ETS-related contaminant, but rather how to obtain accurate quantitative measures of exposure to the entire ETS mixture. The measurement of all components in ETS is not feasible, practical, or even desirable due to limitations in knowledge of the mixture components related to the effects of interest, as well as the feasibility and cost of sampling. It is necessary then to identify a marker (also referred to as a tracer, proxy, indicator, or surrogate) for ETS that will, when measured, accurately represent the frequency, duration, and magnitude of exposure to ETS. These markers can be chemicals measured in the air, biomarkers, models, or simple questionnaires.

There are important issues related to the measurement of a given marker compound to represent exposure to ETS. Ideally, an air contaminant marker for ETS should (1) vary with source strength, (2) be unique to the source, (3) be easily detected in air at low concentrations, (4) be similar in emission rates for a variety of tobacco products, (5) occur in a consistent ratio in air to other ETS components in the complex mix, and (6) be easily, accurately, and cost effectively measured (Leaderer, 1990). The marker can be a specific compound (e.g., nicotine) or much less specific (e.g., respirable suspended particle mass). These criteria for selecting a suitable marker compound are the ideal criteria. In practice, no single contaminant or class of contaminants has been identified that would meet all the criteria. Selection of a suitable marker for ETS is reduced to satisfying as many of the criteria for judging a marker as is practical. In using a marker, it is important to state clearly the role of the marker and to note its limitations.

A number of marker or proxy compounds have been used to represent ETS concentrations in both field and chamber studies. Nicotine, carbon monoxide, 3-ethenylpyridine, nitrogen dioxide, pyridine, aldehydes, nitrous acid, acrolein, benzene, toluene, myosmine, and several other compounds have been used or suggested for use as markers or proxies for the vapor phase constituents of ETS (NRC, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Löfroth et al., 1989; Leaderer and Hammond, 1991; Guerin et al., 1992). Tobacco-specific nitrosamines, particle phase nicotine and cotinine, solanesol, polonium-210, benzo[a]pyrene, potassium, chromium, and respirable suspended particle mass (RSP--particle mass $\leq 2.5\ \mu m$) are among the air contaminants used or suggested for use as markers for particle phase constituents of ETS (NRC, 1986; U.S. DHHS, 1986; Leaderer and Hammond, 1991; Benner et al., 1989; Hammond et al., 1987; Rickert, 1984; Guerin et al., 1992). All the markers employed to date have some problems associated with their use. For example, carbon monoxide, nitrogen oxides, benzene, and RSP have many indoor and outdoor sources other than the combustion of tobacco, while other compounds such as nitrosamines and benzo[a]pyrene are sufficiently difficult to measure (e.g., concentrations in smoking environments are low and the cost of collection and analysis of samples is high) that their use is very limited.

At the present time, vapor phase nicotine and respirable suspended particulate matter are widely and most commonly used as markers of the presence and concentration of ETS for a variety of reasons associated with their ease of measurement, existing knowledge of their emission rates from tobacco combustion, and their relationship to other ETS contaminants.

Vapor phase nicotine, the dominant form of nicotine in ETS (Eudy et al., 1985; NRC, 1986; U.S. DHHS, 1986; Hammond et al., 1987; Eatough et al., 1986; Guerin et al., 1992) accounts for approximately 95% of the nicotine in ETS and is a good marker air contaminant for ETS. It is specific to tobacco combustion and is emitted in large quantities in ETS (NRC, 1981, 1986; U.S. DHHS, 1986; Rickert et al., 1984; Eatough et al., 1990; Guerin et al., 1992). Chamber measurements have shown that nicotine concentrations vary with source strength (Rickert et al., 1984; Hammond et al., 1987; Hammond and Leaderer, 1987; Leaderer and Hammond, 1991) and show little variability among brands of cigarettes, despite variations in MS emissions (Rickert et al., 1984; Leaderer and Hammond, 1991). Field studies have shown that weekly nicotine concentrations are highly correlated with the number of cigarettes smoked (Hammond et al., 1987; Mumford et al., 1989; Thompson et al., 1989; Leaderer and Hammond, 1991). One large field study (Leaderer and Hammond, 1991) showed that weekly nicotine concentrations were strongly correlated with measured RSP levels, as well as with reported number of cigarettes smoked. In this study, the slope of the regression line was 10.8 (standard error of ± 0.72), similar to the RSP/nicotine level seen in chamber studies. Also, the RSP intercept was equal to background levels in homes without smoking ($17.9\ \mu g/m^3 \pm 1.63$) (Leaderer et al., 1990). A comparable study by Miesner et al. (1989) of particulate matter and nicotine in workplaces found a similar ratio between RSP and nicotine. The utility of nicotine as an ETS marker is enhanced by the fact that recent advances in air sampling have resulted in the development of a variety of validated and inexpensive passive and active monitoring methods for measuring nicotine in indoor air environments and for personal monitoring (Hammond et al., 1987; Hammond and Leaderer, 1987; Eatough et al., 1989a; Koutrakis et al., 1989; Muramatsu et al., 1984; Oldaker and Conrad, 1987).

Nicotine is also an attractive marker for the complex ETS air contaminant mix because it and its metabolites, principally cotinine, can serve as biomarkers of ETS exposure. Nicotine and cotinine have long served as markers for active smoking. Over the past several years, measurements of nicotine and cotinine in blood, urine, and saliva have been used extensively as reasonably sensitive biomarkers indicative of exposure to ETS (see Section 3.3.2).

Nicotine is, however, not an ideal ETS marker. One of the potential drawbacks is that vapor-phase nicotine has a high affinity for indoor surfaces. The high adsorption rate of nicotine could decrease its concentration relative to other ETS constituents, particularly ETS-associated particle mass (Eudy et al., 1986; Rickert et al., 1990; Eatough et al., 1989b). This relative decrease in concentration could lead to an underestimation of ETS exposures. The ratio of nicotine to RSP and possibly other ETS constituents would be expected to be most dynamic as the ETS contaminant mix ages (Eatough et al., 1989a). An additional potential problem is that nicotine may be re-emitted from interior surfaces, resulting in measurable concentrations in the absence of active smoking. There have, however, been a number of field studies (see above and Figures 3-4 and 3-7) where nicotine has been used successfully as an ETS marker. These studies would indicate that the uncertainties associated with nicotine in typical indoor environments under normally encountered smoking rates are relatively small. Levels of nicotine in smoking environments have been measured over several orders of magnitude (Figures 3-4 and 3-7), suggesting that the uncertainty associated with its high adsorption rate is small compared to the concentration range. It should also be noted that other gas phase ETS contaminants may exhibit adsorption and reemission properties similar to that of nicotine. Use of nicotine or any other ETS marker must consider the limitations associated with its use.

The combustion of tobacco results in substantial emissions of RSP. One small chamber study using a smoking machine found the average particle emission rate for 15 Canadian cigarettes to be 24.1 mg/cigarette with a range of 15.8-36.0 mg/cigarette (Rickert et al., 1984). A large chamber study using smokers reported an average particle emission rate of 17.1 mg for 12 brands of American cigarettes (Leaderer and Hammond, 1991). This study noted that emission rates among brands are similar. Included in the RSP are a number of compounds of direct health concern, e.g., many of the polycyclic aromatic hydrocarbons and tobacco-specific *N*-nitrosamines (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Tables 3-1 and 3-3, Figure 3-3). There are a number of accepted methods to measure personal RSP exposures and concentrations in indoor environments (Ogden et al., 1990). The available methods permit the accurate measurement of RSP for sampling times ranging from seconds to several days.

Numerous studies of personal exposures to RSP and of RSP levels in indoor environments have shown elevated levels of RSP in environments where smoking was reported (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Leaderer and Hammond, 1991; Turk et al., 1987). One study found a strong correlation between weekly residential RSP levels and reported number of cigarettes smoked (Leaderer and Hammond, 1991). At low smoking and high ventilation rates, however, it may be difficult to separate out the ETS-associated RSP in a background of RSP from other indoor sources (e.g., kerosene heaters) or even from outdoor sources. In using RSP as a marker for ETS, it is important to account for the background RSP level related to other sources before ascertaining the contribution from ETS. Efforts to model ETS exposures for the purpose of assessing risks and the impact of various mitigation measures have often focused on predicting ETS-associated RSP concentrations (e.g., Repace and Lowrey, 1980).

3.3.1.2. *Measured Exposures to ETS-Associated Nicotine and RSP*

3.3.1.2.1. ***Measurements using stationary monitors.*** In the past several years, numerous studies have been conducted in a variety of indoor environments to determine the impact of tobacco combustion on levels of nicotine and RSP. These studies have employed a variety of protocols that used a diversity of air sampling techniques (passive, active, continuous integrative, etc.), sampled over highly varying timeframes (from minutes to several days), and collected highly variable information on factors affecting the measured concentrations (number of cigarettes smoked, volume of building, ventilation rates, etc.). In an attempt to present an overall view of the contribution of ETS to indoor air quality, only the summary results of the measured concentrations of ETS-associated nicotine and RSP will be discussed here. Several reviews of the studies evaluating the impact of ETS on indoor RSP levels have been conducted over the past few years, and a number of recent reports have discussed measured indoor levels of nicotine (e.g., NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Leaderer and Hammond, 1991). Only the indoor levels measured are discussed and summarized. In order to assess exposures, the time in contact with the concentrations would have to be estimated or measured. The reader is referred to those reports and to the individual study reports to acquire more detailed information.

Measured nicotine concentrations in various indoor environments where smoking was noted are summarized in Figure 3-4. The mean concentration, standard deviation, and the maximum and minimum values recorded are presented. Also given in Figure 3-4 are the number of locations in which the measurements were taken and the references in which the data were reported. Elevated nicotine levels were measured in all microenvironments in which smoking was reported. Measured nicotine levels, as would be expected, were highly variable, covering several orders of magnitude.

The home and workplace may represent the most important environments for exposure to ETS because of the amount of time individuals spend there. For the five studies reporting residential levels, average nicotine concentrations in homes where smoking occurs ranged from less than 1 $\mu g/m^3$ (Leaderer and Hammond, 1991) to over 14 $\mu g/m^3$ (Muramatsu et al., 1984). For two of the studies (Leaderer and Hammond, 1991; Marbury et al., 1990) nicotine concentrations represent weekly averages. Actual concentrations in the homes during nonsleeping occupancy (i.e., while smoking would be occurring) would be considerably higher than the levels presented in the table (a factor of 3 or more higher). Workplace nicotine also demonstrated a wide range of concentrations, from near zero to over 33 $\mu g/m^3$. In other environments, nicotine concentrations also demonstrated considerable variability. It is important to note that short-term concentrations

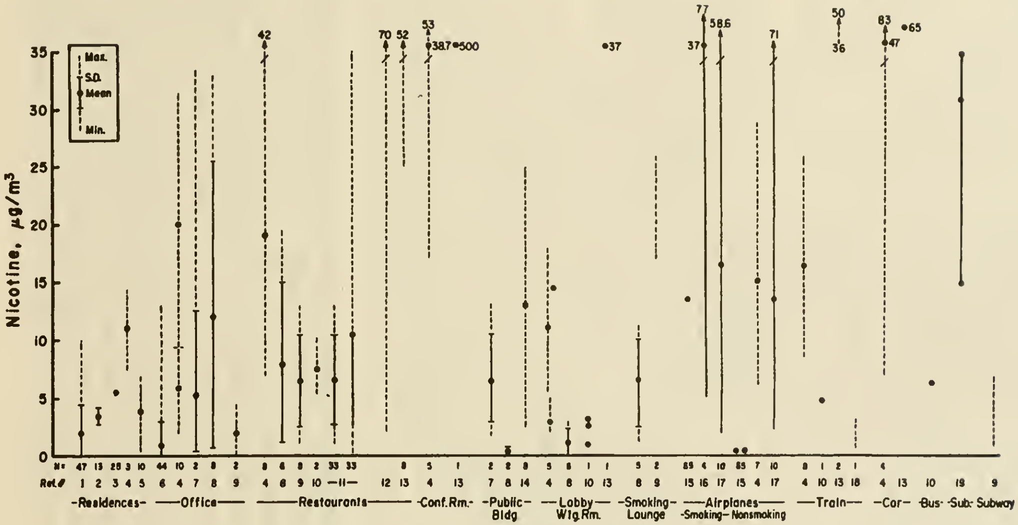


Figure 3-4. Mean, standard deviation, and maximum and minimum nicotine values measured in different indoor environments with smoking occupancy. References from which observations are reported and the number of environments monitored are also given.

REFERENCES FOR FIGURES 3-4 AND 3-5

Figure 3-4

1. Leaderer and Hammond, 1991
2. Mumford et al., 1989
3. Marbury et al., 1990
4. Muramatsu et al., 1984
5. Coultas et al., 1990b
6. Weber and Fischer, 1980
7. Vaughan and Hammond, 1990
8. Leaderer, 1989
9. Miesner et al., 1989
10. Hinds and First, 1975
11. Oldaker et al., 1990
12. Coghlin et al., 1989
13. Badre et al., 1978
14. Higgins, 1987
15. Nagda et al., 1990
16. Eatough et al., 1990
17. Mattson et al., 1989
18. Harmsden and Effenberger, 1957
19. Cano et al., 1970

Figure 3-5

1. Brunekreef and Boleij, 1982
2. Hawthorne et al., 1984
3. Moschandreas, 1981
4. Nitschke et al., 1985
5. Parker et al., 1984
6. Spengler et al., 1981
7. Spengler et al., 1985
8. Leaderer et al., 1990
9. Lebret et al., 1990
10. Coultas et al., 1990b
11. Turk et al., 1987
12. Weber and Fischer, 1980
13. Sterling and Sterling, 1983
14. Nelson et al., 1982
15. Quant et al., 1982
16. Repace and Lowery, 1980
17. Repace and Lowery, 1982
18. Leaderer, 1989
19. First, 1984
20. Oldaker et al., 1990
21. Ishizu, 1980
22. Husgafvel-Pursiainen et al., 1986
23. Eatough et al., 1990
24. Neal et al., 1978
25. Nagda et al., 1990
26. U.S. Department of Transportation, 1971
27. Elliot and Rowe, 1975

(on the order of minutes) are likely to show considerably more variability, resulting in considerably higher short-term peak exposures.

A substantial number of studies examining the impact of tobacco combustion on concentrations of RSP in various indoor environments have been reported. Many of these studies have reported outdoor RSP concentrations and indoor RSP levels without smoking as well as concentrations when smoking occurs. These studies are summarized in Figure 3-5. Outdoor and indoor RSP levels for each of the studies as well as the smoking-associated RSP measurements are shown. The sampling time for the presented data ranged from one minute to over several days. A major portion of the data is for the residential indoor environment. Where smoking is reported, RSP levels are considerably higher than RSP levels outdoors or indoors without smoking. RSP levels associated with smoking, like those for nicotine, demonstrated considerable variability ranging from a few $\mu g/m^3$ to over 1 mg/m^3. Workplace RSP levels associated with smoking occupancy are comparable to residential RSP levels.

In one large residential study, both ETS-associated nicotine and RSP levels were found to be highly correlated ($r = 0.84$; $p < 10^{-5}$) with reported number of cigarettes smoked (Leaderer and Hammond, 1991). This study found that, consistent with chamber data, measured nicotine concentrations predicted the contribution to residential RSP levels from tobacco combustion (Figure 3-6). The data in Figure 3-6 might be used to estimate the RSP levels associated with tobacco combustion from the nicotine levels shown in Figure 3-4. The predictive equation, along with the standard errors, is given in the figure and figure legend. In a study of the impact of smoking on residential levels of RSP and nicotine and of urinary cotinine levels in nonsmoking occupants involving 10 homes, a correlation of 0.54 between residential levels of RSP and nicotine was found (Coultas et al., 1990b).

Indoor levels of nicotine and RSP associated with the combustion of tobacco are a function of several factors related to the generation, dispersal, and removal of ETS in enclosed environments (see Section 3.3.1). Thus, measured levels of these air contaminants indicate a wide range of concentrations (Figures 3-1 and 3-2). Figures 3-7 and 3-8 present a summary of the range of nicotine and ETS-associated particle concentrations measured by type of environment. The figures present the range of average values reported for each study and the minimum and maximum values reported. Only studies reporting sampling times over 4 hours were included in the residential and office summaries in Figures 3-7 and 3-8, because the averaging time is more likely to represent the exposures associated with occupancy time (this included most of the studies for residential spaces shown in Figures 3-4 and 3-5). Since occupancy time in other environments (e.g., restaurants) is likely to be much shorter, averaging times on the order of minutes or greater were considered for the other indoor environments presented in the figures. Indoor particulate

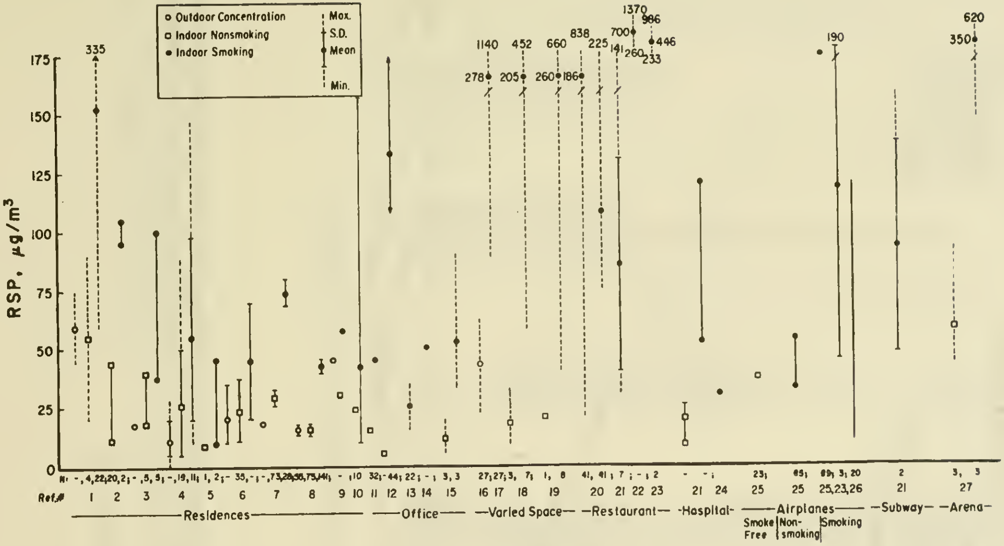


Figure 3-5. Mean, standard deviations, and maximum and minimum concentrations of respirable suspended particle mass (RSP) measured in different indoor environments for smoking and nonsmoking occupancy. Also shown are outdoor concentrations. References from which observations are reported and the number of environments monitored are also given.

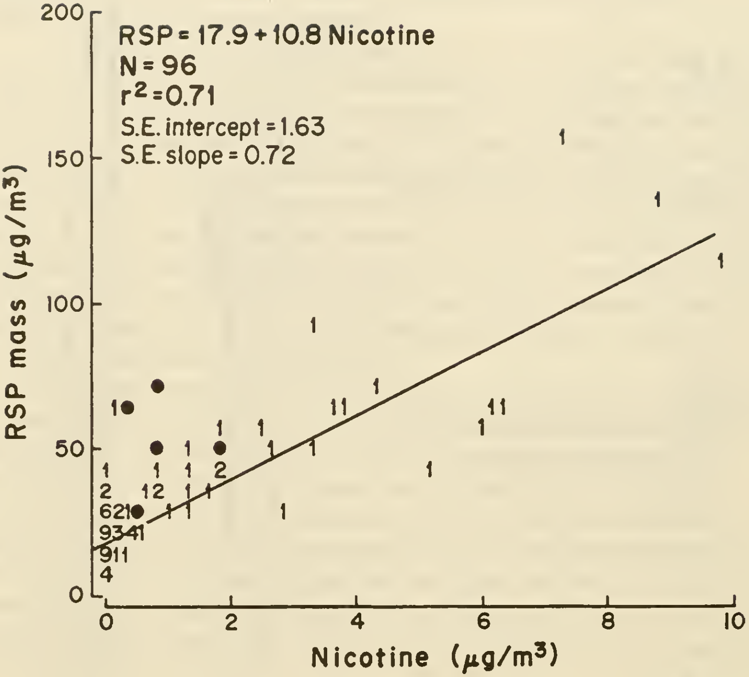


Figure 3-6. Week-long respirable suspended particle mass (RSP) and nicotine measurements in 96 residences with a mixture of sources. Numbers 1-9 refer to the number of observations at the same concentration.

Source: Leaderer and Hammond, 1991.

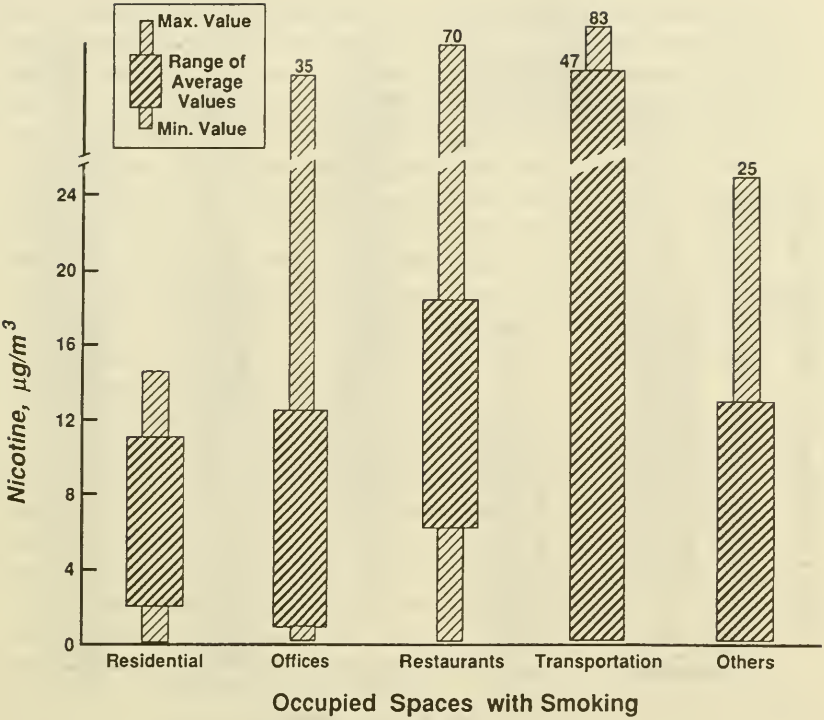


Figure 3-7. Range of average nicotine concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-4. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

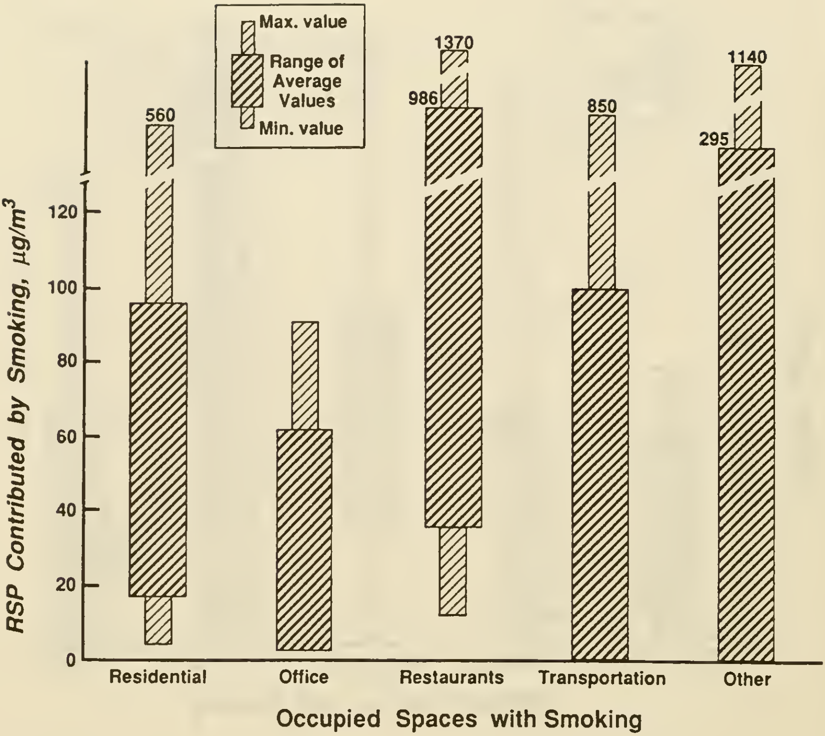


Figure 3-8. Range of average respirable suspended particle mass (RSP) concentrations and range of maximum and minimum values measured by different indoor environments for smoking occupancy from studies shown in Figure 3-5. RSP values represent the contribution to background levels without smoking. Background levels were determined by subtracting reported indoor concentrations without smoking. Only those studies with sampling times of 4 hours or greater are included in the residential and office indoor environment summaries.

levels associated with smoking occupancy (Figure 3-8) were calculated by subtracting particle levels for nonsmoking occupancy (presented in the studies) from the smoking occupancy levels. Thus, the increase in particle mass concentrations associated with ETS is presented in Figure 3-8. Indoor RSP levels in residences without smokers are typically in the range of 10-25 $\mu g/m^3$, while background office levels are somewhat lower (Figure 3-5).

The summary nicotine data (Figure 3-7) suggest that average nicotine values in residences with smoking occupancy will range from 2 to approximately 10 $\mu g/m^3$, with high values up to 14 $\mu g/m^3$ and low values down to 0.1 $\mu g/m^3$. Offices with smoking occupancy show a range of average nicotine concentrations similar to that of residences, but with considerably higher maximum values. The data from other indoor spaces suggest considerable variability, particularly in the range of maximum values. The cumulative distribution of weekly nicotine measured in one study (Leaderer and Hammond, 1991) for a sample of 96 homes, with the levels for smoking occupancy emphasized, is shown in Figure 3-9.

Particle mass concentrations in smoker-occupied residences show average increases of from 18 to 95 $\mu g/m^3$, while the individual increases can be as high as 560 $\mu g/m^3$ or as low as 5 $\mu g/m^3$ (Figure 3-8). Figure 3-10 (Leaderer and Hammond, 1991) highlights the distribution of weekly RSP concentrations for residences with smoking occupancy. In that study, smoking residences had RSP concentrations approximately 29 $\mu g/m^3$ higher than nonsmoking homes. Concentrations in offices with smoking occupancy will be on average about the same as those in residences. Interestingly, in a large and possibly the most comprehensive study of particle mass concentrations associated with smoking and nonsmoking sites in office buildings (Turk et al., 1987), the geometric mean concentration for RSP in 32 smoking sites was 44 $\mu g/m^3$ while the geometric mean for 35 nonsmoking sites was 15 $\mu g/m^3$. The difference of 29 $\mu g/m^3$ is the same as that found for smoking and nonsmoking residences (Figure 3-10). Restaurants, transportation, and other indoor spaces with smoking occupancy will result in a considerably wider range of average, minimum, and maximum increases in particle concentrations than the residential or office environments.

As noted earlier, indoor air contaminant concentrations are the result of the interaction of a number of factors related to the generation, dispersal, and elimination of the contaminants. Source use is no doubt the most important factor. Few studies have measured contaminant concentrations as a function of the smoking rate in residences or offices, but some data are available. One study estimated an average weekly contribution to residential RSP of 2-5 $\mu g/m^3$ per cigarette (Leaderer et al., 1990), while another study estimated that a pack-a-day smoker would add 20 $\mu g/m^3$ to residential levels (Spengler et al., 1981). Coultas et al. (1990b) estimated

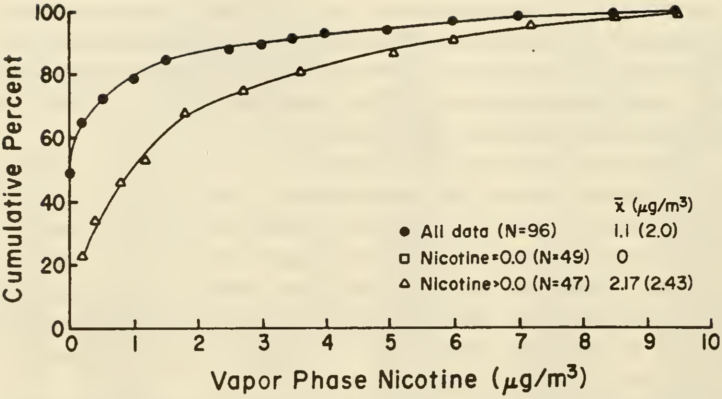


Figure 3-9. Cumulative frequency distribution and arithmetic means of vapor-phase nicotine levels measured over a 1-week period in the main living area in residences in Onondaga and Suffolk Counties in New York State between January and April 1986.

Source: Leaderer and Hammond, 1991.

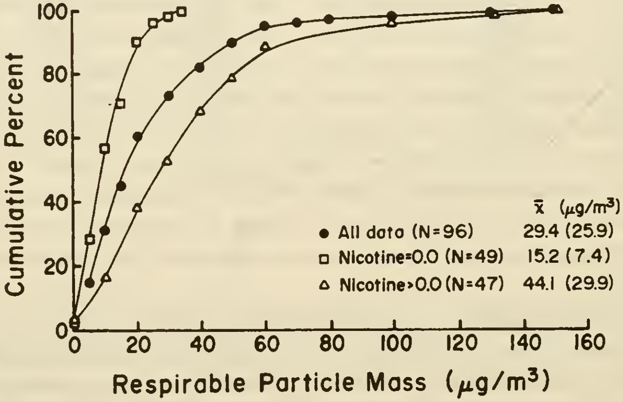


Figure 3-10. Cumulative frequency distribution and arithmetic means of respirable suspended particle mass levels by vapor-phase nicotine levels measured over a 1-week period in the main living area in residences in Onondaga and Suffolk Counties in New York State between January and April 1986.

Source: Leaderer and Hammond, 1991.

that one or more smokers in a home added approximately 17 $\mu g/m^3$ to the residential RSP level. Variations in residential RSP levels as a function of the number of smokers and over a period of several months are demonstrated in Figure 3-11 (Spengler et al., 1981). An association between the reported number of cigarettes and weekly residential nicotine and RSP levels for a sample of 96 homes (Leaderer and Hammond, 1991) is shown in Figure 3-12a and 3-12b. Smoking clearly increases indoor concentrations of both nicotine and particle mass, and residential levels of both nicotine and particle mass increase with increasing levels of smoking. Since nicotine and particle mass are proxies for the complex ETS contaminant mix, other ETS air contaminants, including the toxic and carcinogenic contaminants, should, similarly, be elevated with smoking occupancy. This elevation for selected contaminants is shown in Figure 3-3 and Table 3-3, and for a wider range of contaminants in other publications (NRC, 1986; U.S. DHHS, 1986; Guerin et al., 1992; Turk et al., 1987; Brunnemann et al., 1992).

Children have been identified as a particularly sensitive group at health risk from exposure to ETS in the residential indoor environment (NRC, 1986; U.S. DHHS, 1986). One study has measured smoking status of the parents and weekly nicotine concentrations in the activity rooms and bedrooms of 48 children under the age of 2 years (Marbury et al., 1990). The results, shown

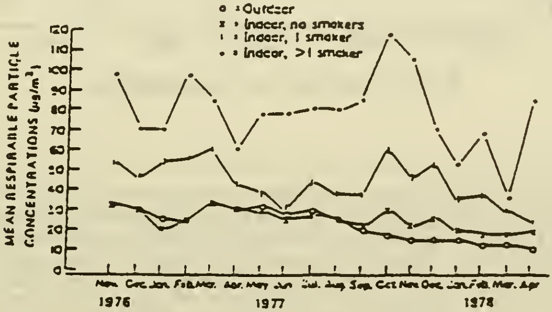


Figure 3-11. Monthly mean respirable suspended particle mass (RSP) concentrations in six U.S. cities.

Source: Spengler et al., 1981.

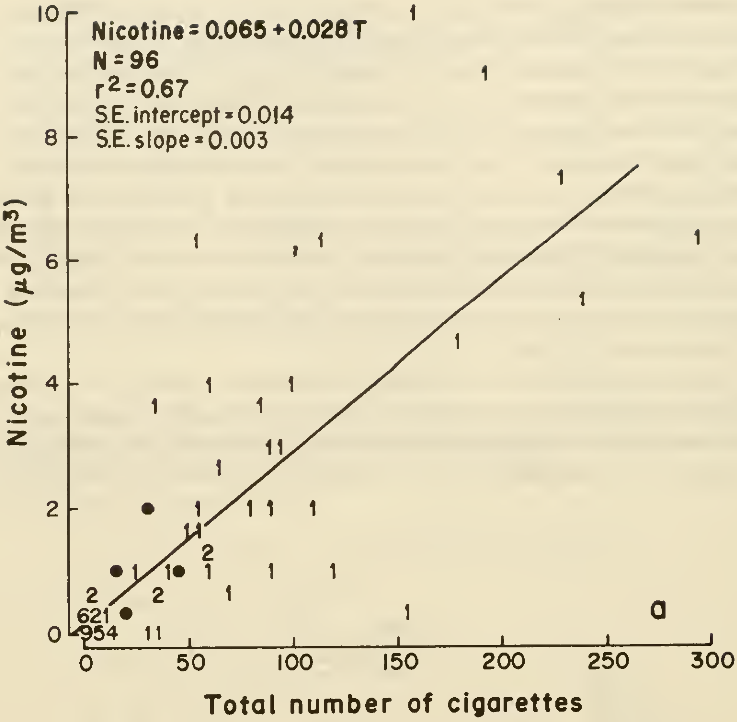


Figure 3-12a. Week-long nicotine concentrations measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk Counties in New York State between January and April 1986. For panel (a), the standard errors for the intercept and slope are 0.014 and 0.002, respectively. For panel (b), the standard errors for the intercept and slope are 2.1 and 0.03, respectively.

Source: Leaderer and Hammond, 1991.

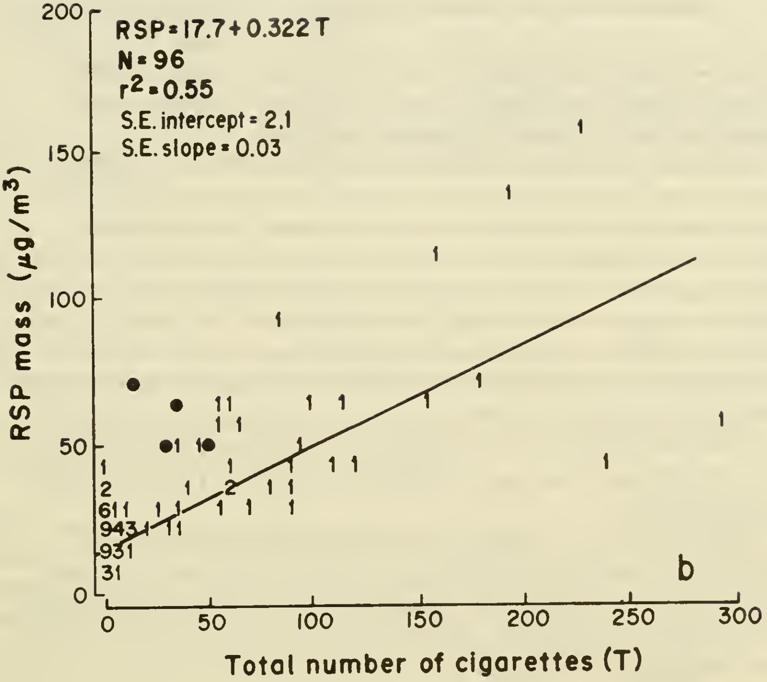


Figure 3-12b. Week-long respirable suspended particle mass (RSP) concentrations measured in the main living area of 96 residences versus the number of questionnaire-reported cigarettes smoked during the air-sampling period. Numbers 1-9 refer to the number of observations at the same concentrations. Closed circles indicate that cigar or pipe smoking was reported in the houses, with each cigar or pipe smoked set equal to a cigarette. Data from residences in Onondaga and Suffolk Counties in New York State between January and April 1986. For panel (a), the standard errors for the intercept and slope are 0.014 and 0.002, respectively. For panel (b), the standard errors for the intercept and slope are 2.1 and 0.03, respectively.

Source: Leaderer and Hammond, 1991.

in Table 3-4, indicate that activity and bedroom concentrations of nicotine in the children's homes increase with the number of cigarettes reported smoked in the home by parents. Concentrations also increased with the number of reported smokers in the household. Correlation coefficients over 0.7 were calculated between nicotine concentrations and number of cigarettes smoked. Exposure of children to ETS is covered in greater detail in Chapter 8.

It is important to note that while measurements of nicotine and ETS-associated RSP are good indicators of the contribution of ETS to air contaminant levels in indoor environments, their measurement does not directly constitute a measure of total exposure. The concentrations measured in all indoor environments have to be combined with time-activity patterns in order to determine average exposure of an individual as the sum of the concentrations in each environment weighted by the time spent in that environment. Both the home and the work environment (those without policies restricting smoking) have highly variable ETS concentrations, with the ranges largely overlapping. Which environment is most important in determining total exposure will vary with individual circumstances (e.g., a person who lives in a nonsmoking home but works in an office with smokers will receive most ETS exposure at work, but for those exposed both at home and at work, the home may be more important because, over the course of a week, more time is generally spent at home).

An additional issue to be considered is how well the general indoor concentrations represent exposures of individuals who may be directly exposed to the SS plume of ETS. Small children, particularly infants, held by smoking parents may receive exposures considerably higher than those predicted from concentrations reported for indoor spaces. Special consideration must be given to these significant subpopulations.

3.3.1.2.2. ***Personal monitors.*** Personal monitoring allows for a direct integrated measure of an individual's exposure. Personal air monitoring employs samplers (worn by individuals) that record the integrated concentration of a contaminant to which individuals are exposed in the course of their normal activity for time periods of several hours to several days. The monitors can be active (employing pumps to collect and concentrate the air contaminant) or passive (working on the principal of diffusion). As with biomarkers, personal monitoring provides an integrated measure of exposure to air contaminants across a number of environments where an individual spends time but does not provide direct information on concentrations of the air contaminant of interest in individual environments or on the level of exposure in each environment unless samples are taken in only one environment or are changed with each change of environment. Supplemental

Table 3-4. Weekly average concentrations of each measure of exposure by parental smoking status in the cross-sectional study, Minnesota, 1989

	Smoking status				
	Non-smokers	Light smokers	Father only	Mother only	Both parents
Number of subjects	23	4	8	6	7
Total cigarettes (no./week)	0.9	28.8	68.6	58.8	227.6
Activity room nicotine ($\mu g/m^3$)	0.15	0.32	2.45	5.50	12.11
Bedroom nicotine ($\mu g/m^3$)	-	0.30	1.21	2.66	5.32

information (air monitoring of spaces, time-activity patterns, etc.) is needed to determine the contribution of each microenvironment to total exposure.

Relatively few studies have measured personal exposures to ETS-associated nicotine and RSP for nonsmoking individuals. The few reported studies of personal exposure to nicotine are summarized in Table 3-5. Personal exposures associated with specific indoor environments are presented. Indoor environments include the nonindustrial workplace, homes, restaurants, public buildings, and transportation-related indoor spaces. Table 3-5 highlights the wide range of indoor environments in which ETS exposures take place and the wide range of personal exposures encountered in those environments. It is important to note, however, that relatively few observations are available and that observations for nonworkplace nicotine exposures are dominated by the Japanese data (Muramatsu), which may not be representative of personal exposures in the United States. Because the data are limited, specific conclusions about the contribution of different indoor environments to personal nicotine exposures associated with passive smoking cannot be drawn. The data do indicate, however, that a wide range of exposures to ETS takes place in a variety of indoor environments where smoking is permitted. The data also indicate that occupational and residential environments are important sources of exposure to ETS because of the levels encountered, which are comparable, and the amount of time individuals spend in them.

Studies of personal exposure to RSP of nonsmoking individuals that have attempted to stratify the collected data by ETS exposure are shown in Table 3-6. Three of the five studies represent exposures integrated over several different microenvironments (residential, public

Table 3-5. Studies measuring personal exposure to airborne nicotine associated with ETS for nonsmokers

Study	Setting	Subject	N	Nicotine, $\mu g/m^3$ X(±SD)	Nicotine, $\mu g/m^3$ Range	Comments
Mattson et al., 1989	Airplane	Attendants	16	4.7 (±4.0)	0.1-10.5	4 attendants on 4 flights
Schenker et al., 1990	Railroad	Clerks	40	6.9		Samples collected over work shifts
Coultas et al., 1990a	Workplace	Nonindustrial	15	20.4 (±20.6)	-	
Muramatsu et al., 1984	Office	Volunteers	10	21.1		Calculated from data presented
	Laboratory		8	5.8		
	Conference room		5	38.7		
	Home		3	11.2		
	Hospital lobby		1	3.0		
	Hotel lobby		4	11.2		
	Restaurant		15	26.0		
	Transportation		22	21.7		
Muramatsu et al., 1984	Office	Volunteers	3	6.9		Calculated from data presented
	Home		7	7.0		
	Restaurant		15	28.2		
	Car		7	40.0		
	Public transportation		1	11.4		

Table 3-6. Studies measuring personal exposure to particulate matter associated with ETS for nonsmokers

		Number of subjects			Particle mass, μg/m^3		Particle mass due to ETS
Study	Setting	Total	No ETS exp.	ETS exp.	X (±SD)	Range	μg/m^3
Spengler et al., 1981	24-hr. day	45			NR	NR	20[a]
Spengler et al., 1985	24-hr. day	101			NR	NR	
			28		NR	NR	28[a]
				73	NR	NR	
Sexton et al., 1984	24-hr. day	48			NR	NR	
			NR		31.7	NR	18.4[1]
				NR	50.1	NR	
Coultas et al., 1990a	Workplace	15			63.9±41.5	4.0-145.8	
			1		4.0		64[2]
				14	68.2±39.5	14.7-145.8	
Schenker et al., 1990	Workplace				86		[3]

[1] Calculated by authors from the regression line.
[2] Calculated from data presented, after the method of Leaderer and Hammond (1991).
[3] Calculated from nicotine exposure, after the method of Leaderer and Hammond (1991).

NR = not reported.

buildings, occupational, etc.), while two studies report exposures for the workplace only. Individuals reporting exposure to ETS have substantially higher integrated exposures to RSP than those reporting no exposure. Passive smoke exposure resulted in increases in personal RSP exposures of 18-64 $\mu g/m^3$. It is difficult to assess the ETS contribution to personal RSP levels for each indoor environment for the 24-hour RSP personal exposures. The contribution of each indoor environment must be substantially higher than the 24-hour averages presented, because exposures presumably did not occur during sleeping hours or in all microenvironments. Table 3-6 demonstrates that the contribution of ETS-related RSP in the work environment to personal exposure is important and variable.

The most extensive study of personal exposure to RSP clearly demonstrates the impact on RSP levels from ETS (Spengler et al., 1985). In this study, outdoor, indoor, and personal 24-hour concentrations of RSP (particle diameter $\leq 3.5\ \mu m$) were obtained for a sample of 101 nonsmoking individuals. Of the 101 nonsmokers, 28 persons reported some exposure to ETS in either the home or workplace, while 73 reported no ETS exposure. The cumulative frequency distributions of RSP for the ETS-exposed and non-ETS-exposed individuals and measured outdoor levels are shown in Figure 3-13. Those reporting ETS exposure had mean personal RSP levels 28 $\mu g/m^3$ higher than those reporting no ETS exposure (Table 3-6). A larger variation in RSP concentrations was also seen for those reporting ETS exposure.

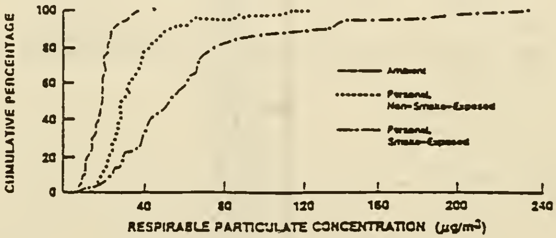


Figure 3-13. Cumulative frequency distribution of respirable suspended particle mass (RSP) concentrations from central site ambient and personal monitoring of smoke-exposed and nonsmoke-exposed individuals.

Source: Spengler et al., 1985.

3.3.2. Biomarkers of ETS Exposure

Biomarkers of exposure are actually measures of dose or uptake and hence indicators that an exposure has taken place. Biomarkers, within the context of assessing exposure to air contaminants, refer to cellular, biochemical, or molecular measures obtained from biological media such as human tissues, cells, or fluids that are indicative of human exposure to air contaminants (NRC and Committee on Biological Markers, 1986; NRC, 1986; Hulka et al., 1990). The relationship between the biomarker and exposure, however, is complex and varies as a function of several factors, including environmental factors and the uptake, distribution, metabolism, and site and mode of action of the compound or compounds of interest.

Ideally, a biomarker of exposure for a specific air contaminant should be chemically specific, have a long half-life in the body, be detectable in trace quantities with high precision, be measurable in samples easily collected by noninvasive techniques, be inexpensive to assay, be either the agent associated with the effects or strongly associated with the agent of interest, and be quantitatively relatable to a prior exposure regimen. Ideal biomarkers for air contaminants, like markers for complex mixtures, do not exist.

Numerous biomarkers have been proposed as indicators for ETS (e.g., thiocyanate, carboxyhemoglobin, nicotine and cotinine, *N*-nitrosoproline, aromatic amines, protein or DNA adducts) (NRC, 1986; U.S. DHHS, 1986). While these biomarkers demonstrate that an exposure has taken place, they may not be directly related to the potential for developing the adverse effect under study (i.e., not the contaminant directly implicated in the effect of interest), they can show considerable variability from individual to individual, and they represent only fairly recent exposure (potentially inadequate for chronic outcomes). Furthermore, some of these markers may not be specific to ETS exposure (e.g., carboxyhemoglobin) while others (e.g., thiocyanate) may not be sensitive enough for ETS exposures.

Nicotine and its metabolite, cotinine, in the saliva, blood, and urine are widely used as biomarkers of active smoking and exposure to ETS and are valuable in determining total or integrated short-term dose to ETS across all environments (NRC, 1986; U.S. DHHS, 1986). Nicotine and cotinine are specific to tobacco and are accurately measured by gas chromatography, radioimmunoassay, or high pressure liquid chromatography in concentrations down to 1 ng/mL. Nicotine has a half-life of about 2 hours in the blood and is metabolized to cotinine and excreted in the urine. The short half-life of nicotine makes it a better indicator of very recent exposures than of integrated exposure.

Cotinine in saliva, blood, and urine is the most widely accepted biomarker for integrated exposure to active smoking or ETS (NRC, 1986; U.S. DHHS, 1986). Cotinine is the major metabolite of nicotine, is specific to tobacco, and has a longer half-life for elimination from the body. The elimination half-life in smokers is approximately 20 hours (range of 10 to 37 hours), but it is typically longer in nonsmokers with ETS exposure, particularly in children (Figure 3-14) (Collier et al., 1990; Elliot and Rowe, 1975; Goldstein et al., 1987; Etzel et al., 1985; Greenberg et al., 1984). The half-life of cotinine makes it a good indicator of integrated ETS exposure over the previous day or two. Laboratory studies of nonsmokers exposed to acute high levels of ETS over varying times have shown significant uptake of nicotine by the nonsmokers and increases in their cotinine levels (NRC, 1986; U.S. DHHS, 1986; Hoffman et al., 1984; Russell and Feyerabend, 1975).

Cotinine, however, is not an ideal biomarker for ETS, and caution in its use has been suggested (Idle, 1990). Cotinine is only one of the metabolites of nicotine (trans-3'-hydroxycotinine has recently been identified as the major metabolite [Neurath et al., 1988]), and it shows considerable intersubject variability in controlled nicotine exposure studies (Idle, 1990). The assumption that nicotine is specific to tobacco has recently been questioned (Idle, 1990; Sheen, 1988; Castro and Monji, 1986; Davis et al., 1991). Plant sources other than tobacco, primarily from the Solanaceae family, which are common dietary components have been suggested as sources (e.g., eggplant, tomato, and green pepper). It has been suggested that nicotine in food is a natural defense against bacteria, fungi, insects, and animals (Ames, 1983).

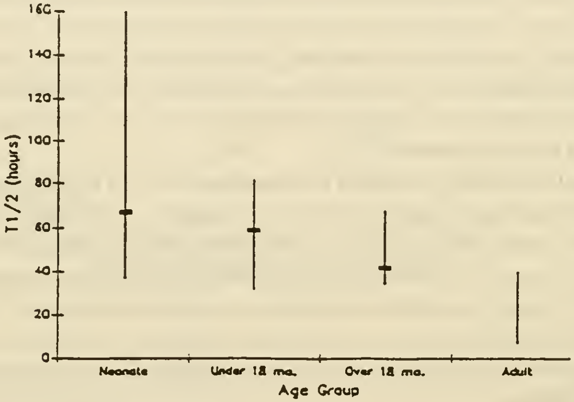


Figure 3-14. Average cotinine $t_{1/2}$ by age groups.

Source: Collier et al., 1990.

Tea has been identified as a particularly high source of dietary nicotine (Sheen, 1988). The impact of dietary nicotine, particularly tea, on cotinine levels of nonsmokers was evaluated in a study of 3,383 men and women 40-59 years of age as part of the Scottish Heart Health Study (Tunstall-Pedoe et al., 1991). The study found a small but inconsistent effect on serum cotinine levels with consumption of 10 or more cups of tea per day with no effect for consumption rates at fewer than 10 cups per day. The authors concluded that "cotinine levels in true nonsmokers reflect far more the nicotine in inhaled ambient tobacco smoke than they do nicotine in tea."

In the most detailed evaluation of nicotine in food, Davis et al. (1991) measured nicotine in a number of teas and foods. They found nicotine levels ranging from less than detectable to 285 ng/g wet weight. The authors calculated that with consuming average quantities of tomatoes, potatoes, cauliflower, and black tea, the average contribution to urinary cotinine levels would be 0.6 ng/mL. High consumption of the foods and tea might result in a maximum urinary cotinine level of 6.2 ng/mL. The average contribution of dietary nicotine intake to urinary cotinine levels might be expected to be below 1 ng/mL and somewhat higher under conditions of high consumption of nicotine-containing foods.

Several population-based studies examined cotinine levels in smokers, nonsmokers reporting passive smoke exposure, and nonsmokers reporting no passive smoke exposure (NRC, 1986; U.S. DHHS, 1986; Greenberg et al., 1984; Wald et al., 1984; Wald and Ritchie, 1984; Jarvis et al., 1985; Coultas et al., 1987; Riboli et al., 1990; Cummings et al., 1990; Tunstall-Pedoe et al., 1991). These studies found that exposure to ETS is highly prevalent even among those living with a nonsmoker (e.g., Cummings et al., 1990). Saliva, serum, and urine cotinine levels in ETS-exposed nonsmokers are generally higher than those in nonsmokers reporting no ETS exposure, and levels of cotinine are considerably higher in smokers than those in nonsmokers passively exposed (e.g., Table 3-7). Cotinine levels in nonsmokers exposed to ETS are approximately 1% of the levels in active smokers. Cotinine levels of nonsmokers have been found to increase with self-reported ETS exposure (e.g., Figures 3-15 and 3-16).

In a 10-country study of ETS exposure of 1,369 nonsmoking women (Riboli et al., 1990), average urinary levels of cotinine/creatinine by country ranged from approximately 2.5 ng/mg for Shanghai to approximately 14 ng/mg for Trieste. Eighty percent of those sampled had a detectable level of cotinine. Statistically significant differences were observed between centers with lowest values observed in Honolulu, Shanghai, and Chandigarh and the highest values in Trieste, Los Angeles, and Athens. This study also found an increase in cotinine/creatinine levels from the group of women reporting no ETS exposure either at home or work (lowest exposure) to the group reporting ETS exposure both at home and at work, the highest exposure group

Table 3-7. Approximate relations of nicotine as the parameter between nonsmokers, passive smokers, and active smokers

Nicotine/cotinine	Nonsmokers without ETS exposure (N = 46)		Nonsmokers with ETS exposure (N = 54)		Active smokers (N = 94)
	Mean value	% of active smokers' value	Mean value	% of active smokers' value	Mean value
Nicotine (ng/mL):					
in plasma	1.0	7.0	0.8	5.5	14.8
in saliva	3.8	0.6	5.5	0.8	673
in urine	3.9	0.2	12.1[1]	0.7	1,750
Cotinine (ng/mL):					
in plasma	0.8	0.3	2.0[1]	0.7	275
in saliva	0.7	0.2	2.5[2]	0.8	310
in urine	1.6	0.1	7.7[2]	0.6	1,390

[1] Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: $p < 0.01$.
[2] Differences between nonsmokers exposed to ETS compared with nonsmokers without exposure: $p < 0.001$.

Source: Jarvis, 1987.

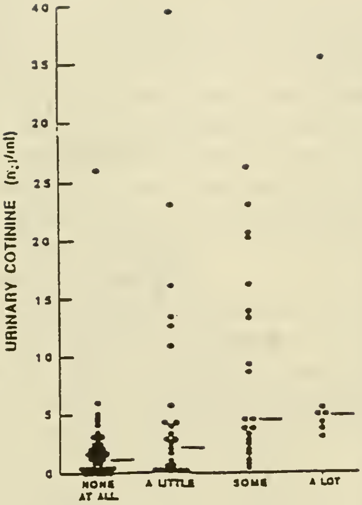


Figure 3-15. Distribution of individual concentrations of urinary cotinine by degree of self-reported exposure to ETS. Horizontal bars indicate median values.

Source: Jarvis and Russell, 1985.

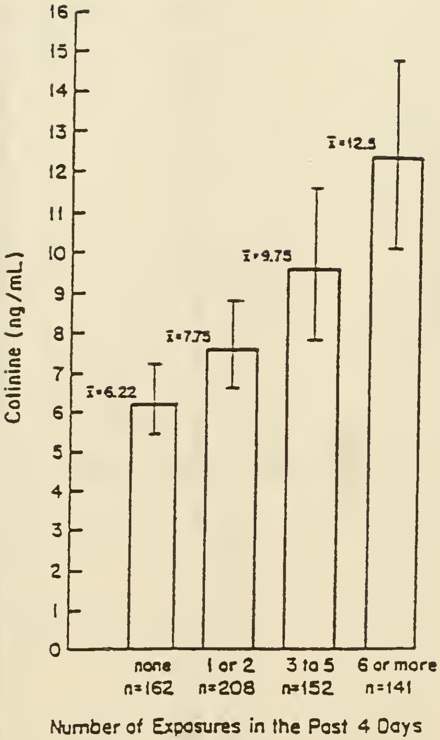


Figure 3-16. Urinary cotinine concentrations by number of reported exposures to tobacco smoke in the past 4 days among 663 nonsmokers, Buffalo, New York, 1986.

Source: Cummings et al., 1990.

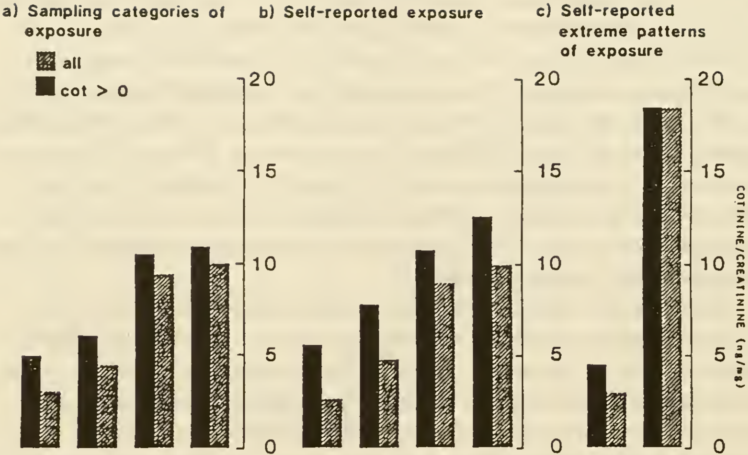
(Figure 3-17). The group of women reporting ETS exposure only at home had cotinine/creatinine levels approximately 60% of those who reported exposure both at home and at work.

Urinary cotinine levels also were found to increase with the number of questionnaire-reported ETS exposures in a group of 663 never-smokers and ex-smokers (Cummings et al., 1990). In that study, 76% of the subjects reported passive smoke exposure in the 4-day period preceding the sampling. Of the total sample, 91% had detectable cotinine levels. Among the 76% reporting ETS exposure, 28% reported exposure at work, 27% at home, 16% in restaurants, 11% at social gatherings, 10% in a car or airplane, and 8% in public buildings. Cotinine levels in this study were also found to vary by month, with the winter months being associated with higher levels and corresponding to higher reported exposures.

Cotinine values in smokers and nonsmokers measured in both the laboratory or field setting show considerable variability due to individual differences in the uptake, distribution, metabolism, and elimination of nicotine. Another issue to be considered in interpreting the field data is that exposure status is determined by respondent self-reporting. This can lead to a misclassification error, which tends to reduce the differences in cotinine levels measured in the ETS-exposed versus non-ETS-exposed groups and to increase the variability in the levels within any exposure category. Within the exposed group, this misclassification error could either increase or decrease the average cotinine levels measured.

It is important to recognize that nicotine and cotinine are actually proxy biomarkers. They may not be the active agents in eliciting the adverse effect under study but merely indicative of the level of passive smoke exposure. Using these measures to estimate cigarette equivalents or determine equivalent active smoking exposure could result in over- or underestimating exposure to individual or classes of compounds that may be more directly related to the health or nuisance effect of concern. Use of different biomarker proxies (e.g., protein adducts) could result in estimates of much larger cigarette equivalent doses.

Nevertheless, nicotine and cotinine levels in ETS-exposed nonsmokers measured in laboratory and field studies have been used to estimate cigarette equivalent exposures and to equate ETS exposures with active smoker exposures (NRC, 1986; U.S. DHHS, 1986; Jarvis, 1989). On an equivalent cigarette basis, an upper-bound estimate of nicotine dose of 2.5 mg/day for a passive smoke exposure has been proposed (Jarvis, 1989). This would translate into the equivalent of about one-fifth of a cigarette per day or about 0.7% of the average smoker's dose of nicotine (cigarette equivalent dose of other toxins or carcinogens would be different--see above). Comparisons of cotinine values in ETS-exposed nonsmokers with those measured in smokers ranged from 0.1% to 2%. One analysis proposed that, on average, nonsmokers' cotinine levels are 0.5%-0.7% of those found in cigarette smokers (Jarvis, 1989). It should be noted that these



EXPOSURE											
AT WORK:		-	+	-	+	-	+	-	+	NO EXPOSURE REPORTED	EXPOSURE FROM ALL SOURCES
AT HOME:		-	-	+	+	-	-	+	+		
ALL	Nº.	405	330	274	293	629	210	359	124	334	36
	MEAN	3.1	4.5	9.5	10.1	2.7	4.8	9.0	10.0	3.0	18.5
COT>0	Nº.	271	268	245	269	429	172	335	117	209	36
	MEAN	5.0	6.1	10.6	11.0	5.6	7.8	10.8	12.6	4.5	18.5

Figure 3-17. Average cotinine/creatinine levels for subgroups of nonsmoking women defined by sampling categories of exposure or by self-reporting exposure to ETS from different sources during the 4 days preceding collection of the urine sample.

Source: Riboli et al., 1990.

estimations are based on a number of assumptions that may not hold (e.g., the half-life of nicotine and cotinine in smokers and nonsmokers being the same).

One of the protein adducts used as a biomarker of active and passive smoking is the 4-aminobiphenyl adduct of hemoglobin. One advantage of hemoglobin adducts is that their half-life is quite long and they will persist through the life of a red blood cell, which is approximately 120 days. Therefore, levels of 4-ABP-Hb adducts reflect exposures over the past several weeks, rather than the day or two of exposure integration reflected by cotinine measurements.

Tobacco smoke is the primary environmental source of 4-aminobiphenyl (its use in the dye industry was discontinued decades ago), and smokers have between 5 and 8 times as much 4-ABP-Hb adducts as nonsmokers (Hammond et al., 1990; Perera et al., 1987; Maclure et al., 1989). That nonsmokers appear to have approximately 10-20% the adduct level as smokers may at first appear to be contradictory to the urinary cotinine ratios of about 1%, but in fact both results are quite consistent with our knowledge of the emissions of various contaminants in mainstream and sidestream smoke. Approximately twice as much nicotine is emitted in sidestream as in mainstream smoke, but about 31 times as much 4-ABP is emitted in SS as in MS. Thus, compared to MS, SS is 15 times more enriched in 4-ABP than in nicotine. Similarly, the ratio of biomarkers in those exposed to ETS compared with smokers is roughly 15 times greater for the biomarker 4-ABP-Hb adducts than for the biomarker cotinine, a metabolite of nicotine.

The above discussions indicate that the cigarette equivalent dose of those exposed to ETS varies with the compound, so that a passive smoker may receive 1% as much nicotine as an active smoker but 15% as much 4-ABP. These examples demonstrate the importance of careful interpretation of biomarkers in estimating doses.

3.3.3. Questionnaires for Assessing ETS Exposures

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective and prospective studies of acute and chronic effects. They are the least expensive method to obtain ETS exposure information for large populations. They can be used to provide a simple categorization of ETS exposure, to determine time-activity patterns of individuals (e.g., how much time is spent in environments where smoking occurs), and to acquire information on the factors or properties of the environment affecting ETS concentrations (e.g., number of cigarettes smoked, size of indoor environments, subjective evaluation of level of smokiness). The time-activity pattern information is combined with measured or estimated concentrations of ETS in each environment to provide an estimate of total exposure. Information on the factors affecting ETS concentrations is used to model or predict ETS levels in those environments.

Questionnaires are used most extensively to provide a simple categorization of potential ETS exposure (e.g., do you live with a smoker?, are you exposed to ETS at your place of work?, how many hours a week are you exposed to ETS?) and to obtain information on possible confounders (e.g., occupational history, socioeconomic status). When used simply to determine a dichotomous exposure (ETS-exposed vs. unexposed), any misclassification tends to bias measures of association toward the null. Thus, any effect that may be present will be underestimated or even may not be detectable. If there are more than two exposure categories (e.g, light, medium, or heavy exposure), the intermediate categories of exposure may be biased either away from or toward the null. Misclassification errors may arise from respondents' (1) lack of knowledge, (2) biased recall, (3) memory failure, and (4) intentional alteration of information. Additionally, there are investigator-based sources of misclassification. Errors may arise if semiquantitative levels are incorrectly imputed to answers; e.g., even if house exposures are higher than occupational exposures on average, for any given individual the ranking may well be reversed from that of the average.

In using questionnaires to assess exposure categories to ETS, to determine time-activity patterns, and to acquire information on the factors affecting concentrations, it is important to minimize the uncertainty associated with the estimate and to characterize the direction and magnitude of the error.

Unlike for active smoking assessment, standardized questionnaires for assessing ETS exposures in prospective or retrospective studies of acute or chronic health or nuisance effects do not exist. Lebowitz et al. (1989) reported on an effort to develop a standardized questionnaire to assess ETS exposure in various indoor environments. This questionnaire, however, has not yet been validated. Questionnaires used to assess ETS exposure typically have been developed for specific studies and have not been validated for general use. There is no "gold standard" with which to validate the questionnaires. Various strategies, however, have been used to assess the validity of diverse types of questionnaires used to assess ETS exposure. Efforts to validate questionnaires have used survey data, air monitoring of nicotine in various microenvironments, and nicotine or cotinine in body fluid samples.

A recent study (Leaderer and Hammond, 1991) of 96 homes using a questionnaire to assess residential smoking and a passive nicotine air monitor found that 13% of the residences reporting no smoking had measurable levels of nicotine while 28% of the residences reporting smoking had nondetectable levels of nicotine. A good level of agreement between questionnaire-reported number of cigarettes smoked and residential levels of ETS-related RSP and nicotine was observed in this study (Figures 3-12a and 3-12b).

Studies (Marbury et al., 1990; Coghlin et al., 1989; Coultas et al., 1987, 1990a, 1990b; Riboli et al., 1990; Cummings et al., 1990) comparing various measures of ETS exposure (location of exposure, intensity of exposure, duration of exposure, number of cigarettes smoked, etc.) with cotinine levels measured in physiological fluids generally meet with only moderate success (explained variations on the order of 40% or less). The largest such study (Riboli et al., 1990) was a collaborative effort conducted in 10 countries; correlations in the range of 0.3 to 0.51 ($p < 0.01$) were found between urinary cotinine levels and various measures of exposure derived from questionnaire data. Using cotinine as a biomarker of exposure, studies indicated that a substantial percentage of those reporting no ETS exposure by questionnaire do have measurable exposure. Differences in the uptake, metabolism, and excretion of nicotine among individuals make it difficult to use this measure as a "gold standard" in validating questionnaires. Also, the recent exposure (previous 1-2 days) that is measured by cotinine may differ from usual exposure.

In a study involving 10 homes with 20 nonsmoking and 11 homes with smoking residents, the variability of four markers of ETS exposure (questionnaires, cotinine in saliva and urine, respirable suspended particle mass in air, and nicotine in air) was assessed (Coultas et al., 1990b). Questionnaire-reported exposures explained less than 10% of the variability in air concentrations of suspended particle mass and nicotine, 8% of the variability in urinary cotinine, and 23% of the variability in saliva cotinine. The authors concluded that multiple exposure assessment measurement tools were needed to assess ETS exposure in the home.

In one effort to develop a validated questionnaire (Coghlin et al., 1989), 53 subjects were asked detailed questions about their exposures to ETS, including location of exposures, number of smokers, ventilation characteristics, number of hours exposed, proximity of smokers, and intensity of ETS. They then wore a passive sampler for nicotine for 7 days and recorded the same information regarding each exposure episode in daily diaries. Formulae were developed to score the exposures on both the questionnaire and the diary, and these scores were then correlated to the average nicotine concentrations measured over the 7-day period. Excellent correlation was found ($r^2 = 0.83$ for the questionnaire and 0.90 for the diary). However, the simple questions that have been used most frequently in epidemiologic studies, such as whether a subject lived with a smoker or the number of hours the subject was exposed, were not nearly as well correlated with the measured exposures. These results indicate that reliable questionnaires can be developed, but that those used in most studies in the past will lead to some random misclassification of exposure, and, hence, underestimation of any effect that may be present.

More recently, epidemiologic studies of acute and chronic respiratory effects in children associated with ETS exposure have utilized questionnaires in combination with measurements of cotinine levels in physiologic fluids (Ehrlich et al., 1992; Reese et al., 1992; Etzel et al., 1992).

The studies provide more of a direct link between questionnaire-assessed exposures and objective measures of exposure and disease. Such studies, discussed in Chapter 8, not only provide a means of validating questionnaires but also provide data to establish validation of the risk models used in Chapter 8.

ETS exposures take place across a number of environments, with an individual's total exposure being a function of the amount of time spent in each environment and the concentration in that environment. Questionnaires need to assess exposures across indoor environments. Personal air monitoring provides a method to validate ETS exposure assessment questionnaires and to assess the contribution of each environment to total current exposure.

Personal air monitoring and cotinine measurements in combination with questionnaires have highlighted the importance of obtaining information on spouses' smoking status, smoking at home, smoking at work, smoking in various other indoor environments (social settings, vehicles, public places, etc.), amount of time in environments where smoking occurs, and the intensity of the exposure (Marbury et al., 1990; Coghlin et al., 1989; Coultas et al., 1987, 1990a, 1990b; Riboli et al., 1990; Cummings et al., 1990).

3.4. SUMMARY

ETS is a major source of indoor air contaminants. The ubiquitous nature of ETS in indoor environments indicates that some unintentional inhalation of ETS by nonsmokers is virtually unavoidable. ETS is a dynamic complex mixture of over 4,000 chemicals found in both vapor and particle phases. Efforts to characterize the physical and chemical properties of SS emissions, the principal component of ETS, have found that: (1) MS and SS emissions are qualitatively very similar in their chemical composition, containing many of the same carcinogenic and toxic compounds, (2) several of these compounds, including five known human carcinogens, nine probable human carcinogens, three animal carcinogens, and several toxic agents, are emitted at higher levels in SS than MS smoke (sometimes by an order of magnitude or more); (3) SS emissions of these notable air contaminants demonstrate little variability among brands of cigarettes. The enrichment of several known or suspected carcinogens in SS relative to MS smoke suggests that the SS contaminant mix may be even more carcinogenic than the MS mix, per unit of tobacco burned.

Sidestream emissions, while enriched in several notable air contaminants, are quickly diluted into the environment where ETS exposures take place. Air sampling conducted in a variety of indoor environments has shown that nonsmoker exposure to ETS-related toxic and carcinogenic substances will occur in indoor spaces where there is smoking occupancy. Individuals close to smokers (e.g., an infant in a smoking parent's arms) may be directly exposed to the plume of SS or exhaled MS, and thus be more heavily exposed than indoor measurements from stationary air monitors might indicate.

Given the complex nature of ETS, it is necessary to identify marker or proxy compounds that when measured will allow for the quantification of exposure to ETS. Vapor phase nicotine and respirable suspended particle mass are two such markers that are suitable indicators of exposure to ETS. Nicotine and RSP have been measured in personal monitoring studies and in studies of a variety of indoor environments. The results of these studies clearly demonstrate that reported exposure to ETS, even under the conditions of low frequency, duration, and magnitude, will result in RSP and nicotine values above background. These studies indicate that ETS exposures take place in a wide range of environments (residences, workplaces, restaurants, airplanes, etc.,) where smoking occurs. Indoor levels of RSP and vapor phase nicotine have been shown to vary in a linear fashion with reported tobacco consumption. Nicotine levels measured indoors have ranged from less than 1 $\mu g/m^3$ to over 500 $\mu g/m^3$, while RSP levels have ranged from less than 5 $\mu g/m^3$ to over 1 mg/m^3. Nicotine exposures greater than 100 $\mu g/m^3$ are exceedingly rare; most environments measured have ranged from less than 0.3 (smoke free) to 30 $\mu g/m^3$; bars and smoking sections of planes may reach 50-75 $\mu g/m^3$. Thus, the normal range of ETS exposures is approximately 100-fold: 0.3 to 30 $\mu g/m^3$ for nicotine and from 5 to 500 $\mu g/m^3$ for RSP.

In residences with smoking occupancy, average daily or weekly nicotine values might typically range from less than 1 to 10 $\mu g/m^3$, varying principally as a function of number of smokers or number of cigarettes smoked. Average daily or weekly residential concentrations of ETS-associated RSP could be expected to increase from 18 to 95 $\mu g/m^3$ (added to background levels) in homes where smoking occurs. Like nicotine, ETS-associated RSP increases with increased smoking. Average levels of nicotine and RSP in offices with smoking occupancy are roughly comparable to those in homes.

Cotinine in saliva, blood, and urine, while not an ideal biomarker, is the most widely accepted biomarker of ETS exposure. Cotinine is an excellent indicator that ETS exposure has taken place. It also establishes the link between exposure and uptake. Studies show that cotinine levels correlate with levels of ETS exposure. The available data also indicate that as many as 80% of nonsmokers are exposed to ETS and that there is variability in average exposure levels among nonsmokers in different geographical regions.

Although average cotinine levels are a useful indicator of relative doses of ETS among different groups of nonsmokers, the ratio of cotinine levels in nonsmokers versus smokers may not be indicative of the exposure ratio for the active agents in ETS and MS responsible for the adverse effects. For example, while comparisons of cotinine levels in smokers and nonsmokers have led to estimates that ETS-exposed nonsmokers receive from 0.1 to 0.7% of the dose of nicotine of an average smoker, ETS-exposed nonsmokers may receive 10-20% of the dose of 4-ABP that smokers inhale.

Questionnaires are the most commonly used method to assess exposure to ETS in both retrospective and prospective studies of acute and chronic effects. They have been used not only to establish simple categories of ETS exposure but also to obtain information on activity patterns of exposed individuals and on environmental factors affecting concentrations in different indoor environments. No standardized or validated questionnaires have yet been developed for assessing ETS exposure. A number of studies have compared questionnaire responses to measured air concentrations of nicotine and RSP and to cotinine levels. These efforts have indicated that a significant percentage of individuals reporting no exposure had actually been exposed. In general, questionnaires had moderate success in assessing exposure status and level of exposure. Misclassification errors must be addressed when using questionnaires to assess ETS exposure.

In summary, ETS represents an important source of toxic and carcinogenic indoor air contaminants. The available data suggest that exposure to ETS is widespread, with a wide range of exposure levels.

4. HAZARD IDENTIFICATION I: LUNG CANCER IN ACTIVE SMOKERS, LONG-TERM ANIMAL BIOASSAYS, AND GENOTOXICITY STUDIES

4.1. INTRODUCTION

Numerous epidemiologic studies have conclusively established that the tobacco smoke inhaled from active smoking is a human lung carcinogen (U.S. DHHS, 1982; IARC, 1986). A clear dose-response relationship exists between lung cancer and amount of exposure, without any evidence of a threshold level. It is, therefore, reasonable to theorize that exposure to environmental tobacco smoke (ETS) might also increase the risk of lung cancer in both smokers and nonsmokers.

As documented in the previous chapter, the chemical compositions of mainstream smoke (MS) and ETS are qualitatively similar, and both contain numerous known or suspected human carcinogens. In fact, ETS contains essentially all of the same carcinogens identified in MS, and many of these appear in greater amounts in sidestream smoke (SS), the primary component of ETS, than in MS, per unit tobacco burned (Table 3-1). In addition, both MS and SS have been shown to be carcinogenic in animal bioassays (Wynder and Hoffman, 1967; Grimmer et al., 1988), and MS, SS, and ETS have all been found to be genotoxic in in vitro systems (IARC, 1986). Furthermore, as the previous chapter also describes, exposure assessments of indoor air and measurements of nicotine and cotinine levels in nonsmokers confirm that passive smokers are exposed to and absorb appreciable amounts of ETS that might result in elevated lung cancer risk.

This chapter reviews the major evidence for the lung carcinogenicity of tobacco smoke derived from human studies of active smoking and the key supporting evidence from animal bioassays and in vitro experiments. The evidence from the few animal and mutagenicity studies pertaining specifically to ETS is also presented. The majority of this information has already been well documented by the U.S. Department of Health and Human Services (U.S. DHHS) (1982) and the International Agency for Research on Cancer (IARC) (1986). The current discussion mainly extracts and summarizes some of the important issues and principal studies described in those comprehensive reports.

In view of the abundant and consistent human evidence establishing the carcinogenic potential of active smoking to the lung, the bulk of this chapter focuses on the human data. Although EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a) suggest an extensive review of all evidence pertaining to carcinogenicity, we believe that the large quantity of human cancer studies on both MS and ETS provide the most appropriate database from which to evaluate the lung cancer potential of ETS. Thus, the animal evidence and genotoxicity results are given only limited attention here. Similarly, a discussion of the mutagenicity data for individual smoke components would be superfluous in the context of the overwhelming evidence from other, more pertinent sources and is not included. Extensive reviews of these data can be found in the U.S. DHHS (1982) and IARC (1986) publications. Claxton et al. (1989) provide an assessment of the genotoxicity of various ETS constituents.

4.2. LUNG CANCER IN ACTIVE SMOKERS

Studies of active smoking in human populations from many countries provide direct and incontrovertible evidence for a dose-related, causal association between cigarette smoking and lung cancer. This evidence includes time trends in lung cancer mortality rates associated with increasing cigarette consumption, high relative risks for lung cancer mortality in smokers of both sexes observed consistently in numerous independent retrospective and prospective studies, and dose-response relationships demonstrated with respect to smoking intensity and duration and for all four major histological types of lung cancer.

4.2.1. Time Trends

While the overall cancer death rate in the United States has been fairly stable since 1950, the lung cancer death rate has increased drastically for both males and females (Figures 4-1 and 4-2). Age-adjusted lung cancer mortality rates in men have increased from 11 per 100,000 in 1940 to 73 per 100,000 in 1982, leveling slightly to 74 per 100,000 in 1987 (Garfinkel and Silverberg, 1991). In women, lung cancer mortality rates have risen from 6 per 100,000 in the early 1960's to 28 per 100,000 in 1987 (Garfinkel and Silverberg, 1991).

The striking time trends and sex differences seen in lung cancer mortality rates correlate with historical smoking patterns. Increases in lung cancer death rates parallel increases in cigarette consumption with a roughly 20-year lag time, accounting for the latency period for the development of smoking-induced lung cancer. Males started smoking cigarettes in large numbers during the years around World War I, whereas females did not begin smoking in appreciable numbers until World War II. Cigarette consumption per capita (based on the total population age 18 and older) in the United States rose from 1,085 in 1925 to a high of 4,148 in 1973. In the past two decades, cigarette consumption has decreased to 2,888 in 1989 (Garfinkel and Silverberg, 1991). This decline correlates with the leveling off of lung cancer mortality rates in recent years.

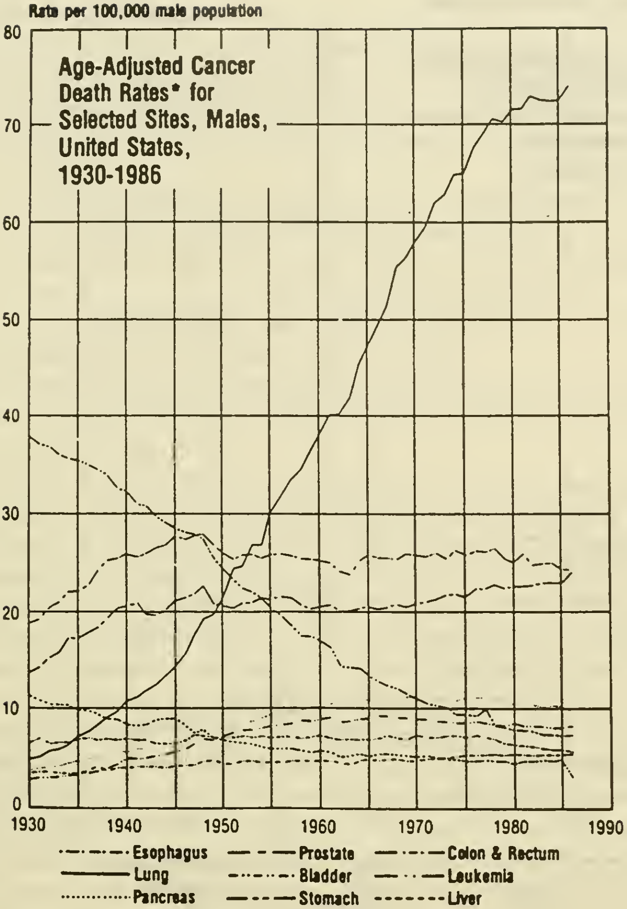


Figure 4-1. Age-adjusted cancer death rates* for selected sites, males, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

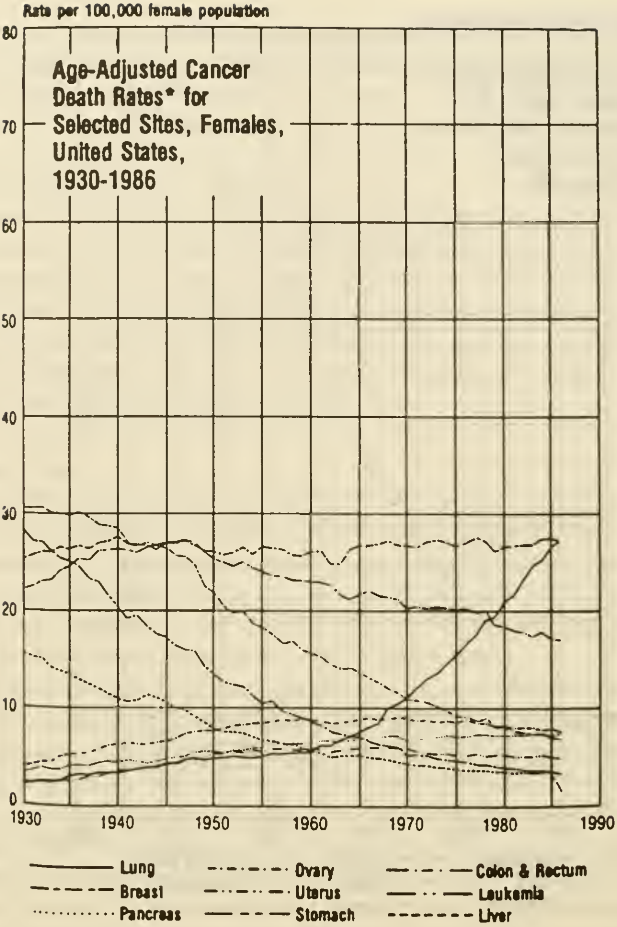


Figure 4-2. Age-adjusted cancer death rates* for selected sites, females, United States, 1930-1986.

*Adjusted to the age distribution of the 1970 U.S. census population.

Source: U.S. DHHS, 1989.

4.2.2. Dose-Response Relationships

More than 50 independent retrospective studies have consistently found a dose-related association between smoking and lung cancer (U.S. DHHS, 1982). Eight major prospective studies from five countries corroborate this association:

- American Cancer Society (ACS) Nine-State Study (white males) (Hammond and Horn, 1958a,b)
- Canadian War Veterans Study (Best et al., 1961; Lossing et al., 1966)
- British Doctors Study (Doll and Hill, 1964a,b; Doll and Peto, 1976; Doll et al., 1980)
- American Cancer Society 25-State Study (Hammond, 1966; Hammond and Seidman, 1980)
- U.S. Veterans Study (Kahn, 1966; Rogot and Murray, 1980)
- California Labor Union Study (Weir and Dunn, 1970)
- Swedish Study (sample of census population) (Cederlöf et al., 1975)
- Japanese Study (total population of 29 health districts) (Hirayama, 1967, 1975a,b, 1977, 1978, 1982, 1985).

Details of the designs of these studies are summarized in Table 4-1. These eight studies together represent more than 17 million person-years and more than 330,000 deaths. Lung cancer mortality ratios from the prospective studies are presented in Table 4-2. Combining the data from the prospective studies results in a lung cancer mortality ratio of about 10 for male cigarette smokers compared with nonsmokers. (Note that these lung cancer mortality ratios underestimate the relative risk of lung cancer to smokers compared with a non-tobacco-smoke-related background risk to nonsmokers [see Chapter 6], given the causal association between ETS exposure and lung cancer in nonsmokers documented in this report.)

This strong association between smoking and lung cancer is further enhanced by very strong and consistent dose-response relationships. A gradient of increasing risk for lung cancer mortality with increasing numbers of cigarettes smoked per day was established in every one of the prospective studies (Table 4-3). Lung cancer mortality ratios for male smokers who smoked more than 20 cigarettes daily were generally 15 to 25 times greater than those for nonsmokers. Marked increases in lung cancer mortality ratios were also seen in all the lowest dose categories. Males who smoked fewer than 10 cigarettes per day had lung cancer mortality ratios 3 to 10 times greater than those for nonsmokers. There is no evidence of a threshold level for the development of smoking-induced lung cancer in any of the studies.

Dose-response relationships with respect to the duration of smoking also have been well established. From the British male physicians study, Peto and Doll (1984) calculated that the

Table 4-1. Main characteristics of major cohort studies on the relationship between smoking and cancer

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
ACS 9-state study	1952	204,547 men [187,783]	Self-administered questionnaire	44 months 11,870 deaths	98.9%
Canadian veterans study	1955-1956	207,397 subjects (aged 30+) [92,000]	Self-administered questionnaire (57% respondents)	6 years 9,491 deaths in men; 1,794 deaths in women	NA
British doctors study	1951	34,440 men (aged 20+)	Self-administered questionnaire (69% respondents)	20 years 10,072 deaths	99.7%
		6,194 women (aged 20+)	Self-administered questionnaire (60% respondents)	22 years 1,094 deaths	99%
ACS 25-state study	1959-1960	1,078,894 subjects, first followup: 440,558 men, 562,671 women (aged 35-84); second followup: 358,422 men, 483,519 women	Self-administered questionnaire	4.5 + 5 years 26,448 deaths in men; 16,773 deaths in women	97.4% in women 97.9% in men in first followup
U.S. veterans study	1954	293,958 men (aged 31-84) [248,046]	Self-administered questionnaire (85% respondents)	16 years 107,563 deaths	Almost 100% ascertainment of vital status; 97.6% of death certificates retrieved
California study	1954-1957	68,153 men (aged 35-64)	Self-administered questionnaire	5-8 years 4,706 deaths	NA

(continued on the following page)

Table 4-1. (continued)

Study	Year of enrollment	Sample size; initial samples; in brackets, population for followup	Source of information on smoking (proportion of respondents)	Duration of followup and no. of deaths	Completeness of followup for mortality
Swedish study	1963	27,342 men, 27,732 women (aged 18-69)	Self-administered questionnaire (89% respondents)	10 years 5,655 deaths (2,968 autopsies)	NA
Japanese study	1965	122,261 men, 142,857 women (aged 40+)	Interview (95% of population in area)	16 years 51,422 deaths	Total

NA = not available.

Source: IARC, 1986.

Table 4-2. Lung cancer mortality ratios--prospective studies

Population	Size	Number of deaths	Nonsmokers	Cigarette smokers
British doctors study	34,000 males 6,194 females	441 27	1.00 1.00	14.0 5.0
Swedish study	27,000 males 28,000 females	55 8	1.00 1.00	7.0 4.5
Japanese study	122,000 males 143,000 females	940 304	1.00 1.00	3.76 2.03
ACS 25-state study	358,000 males 483,000 females	2,018 439	1.00 1.00	8.53 3.58
U.S. veterans study	290,000 males	3,126	1.00	11.28
Canadian veterans study	78,000 males	331	1.00	14.2
ACS 9-state study	188,000 males	448	1.00	10.73
California males in 9 occupations	68,000 males	368	1.00	7.61

Source: U.S. DHHS, 1982.

Table 4-3. Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day--prospective studies

	Men		Women	
Population	Cigarettes smoked per day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25-state study	Nonsmoker	1.00	Nonsmoker	1.00
	1-9	4.62	1-9	1.30
	10-19	8.62	10-19	2.40
	20-39	14.69	20-39	4.90
	40+	18.71	40+	7.50
British doctors study	Nonsmoker	1.00	Nonsmoker	1.00
	1-14	7.80	1-14	1.28
	15-24	12.70	15-24	6.41
	25+	25.10	25+	29.71
Swedish study	Nonsmoker	1.00	Nonsmoker	1.00
	1-7	2.30	1-7	1.80
	8-15	8.80	8-15	11.30
	16+	13.70	16+	--
Japanese study (all ages)	Nonsmoker	1.00	Nonsmoker	1.00
	1-19	3.49	<20	1.90
	20-39	5.69	20-29	4.20
	40+	6.45		
U.S. veterans study	Nonsmoker	1.00		
	1-9	3.89		
	10-20	9.63		
	21-39	16.70		
	≥40	23.70		
ACS 9-state study	Nonsmoker	1.00		
	1-9	8.00		
	10-20	10.50		
	20+	23.40		
Canadian veterans study	Nonsmoker	1.00		
	1-9	9.50		
	10-20	15.80		
	20+	17.30		
California males in 9 occupations	Nonsmoker	1.00		
	about ½ pk	3.72		
	about 1 pk	9.05		
	about 1½ pk	9.56		

Source: U.S. DHHS, 1982.

excess annual incidence rates of lung cancer after 45, 30, and 15 years of cigarette smoking were in the approximate ratio of 100:20:1 to each other. The California and Swedish studies also demonstrated an increasing risk of lung cancer in men with longer smoking duration (Table 4-4).

Four of the prospective studies examined lung cancer mortality in males by age at initiation of smoking and found increasing risk with younger age (Table 4-5). Some of the studies also investigated smoking cessation in men and observed a decrease in lung cancer risk with increasing number of years since quitting smoking (Table 4-6). The Cancer Prevention Study II, a study of 1,200,000 people in all 50 states, reveals a similar trend for women who quit smoking (Figure 4-3). The occurrence of higher lung cancer mortality ratios in the groups with only a few years since cessation as compared with current smokers (Table 4-6 and Figure 4-3) is attributable to the inclusion of recent ex-smokers who were forced to stop smoking because they already had smoking-related symptoms or illness (U.S. DHHS, 1990a). The increased lung cancer risks seen in people who started smoking at a younger age and the decreased risks seen with time since smoking cessation suggest both initiation and promotion capabilities of tobacco smoke components.

Additional dose-response relationships have been derived from consideration of the types of tobacco products used. Pipe and cigar smokers, who inhale less deeply than cigarette smokers, have lower risks of lung cancer than cigarette smokers (Table 4-7). Furthermore, the American Cancer Society 25-state study found decreased risks for lung cancer in males and females who smoked cigarettes with lower tar and nicotine content compared with those who smoked cigarettes with higher tar and nicotine content (Table 4-8), although these decreased risks are still substantially higher than the risk to nonsmokers. Similarly, it has been established that smokers of filtered cigarettes have relatively lower lung cancer risks than smokers of nonfiltered cigarettes (Table 4-9). Filters reduce the amount of tars, and hence a portion of the carcinogenic agents, in the MS inhaled by the smoker. Passive smokers, however, do not share in any benefit derived from cigarette filters (see Chapter 3) and may, in fact, be exposed to greater amounts of ETS if smokers of filtered cigarettes smoke a greater number of cigarettes to compensate for any reduction in nicotine uptake resulting from the filters (U.S. DHHS, 1986).

4.2.3. Histological Types of Lung Cancer and Associations With Smoking

A number of epidemiologic studies have also examined the association between various histological types of lung cancer and smoking. The results of some of these investigations are summarized in Table 4-10. Problems in interpreting the results of such studies include differences in the nomenclature, criteria, and verification of tumor classification; inadequacy of some specimens; and the small size of many of the patient groups, resulting in unstable risk

Table 4-4. Relationship between risk of lung cancer and duration of smoking in men, based on available information from cohort studies

Reference	Duration of smoking (years)	Standardized mortality ratio (no. of observed deaths)	Approximate annual excess death rate (%)[1]
Weir and Dunn (1970)	1-9	1.13	0.002 (0.001)
	10-19	6.45	0.09 (0.05)
	20+	8.66	0.12 (0.08)
	Nonsmokers	1.0	0
Cederlöf et al. (1975)	1-29	1.8 (5)	0.01 (0.008)
	>30	7.4 (23)	0.1 (0.06)
	Nonsmokers	1.0 (7)	0

[1] The mortality ratio among nonsmokers was assumed to be 15.6 per 100,000 per year, as in the American Cancer Society 25-state study. Figures in parentheses were computed by the IARC working group, applying the British doctors' mortality rate among nonsmokers (10.0/100,000 per year).

Source: IARC, 1986.

Table 4-5. Lung cancer mortality ratios for males, by age of smoking initiation--prospective studies

Study	Age of smoking initiation in years	Mortality ratio
ACS 25-state study	Nonsmoker	1.00
	25+	4.08
	20-24	10.08
	15-19	19.69
	Under 15	16.77
Japanese study	Nonsmoker	1.00
	25+	2.87
	20-24	3.85
	Under 20	4.44
U.S. veterans study	Nonsmoker	1.00
	25+	5.20
	20-24	9.50
	15-19	14.40
	Under 15	18.70
Swedish study	Nonsmoker	1.00
	19+	6.50
	17-18	9.80
	Under 16	6.40

Source: U.S. DHHS, 1982.

Table 4-6. Relationship between risk of lung cancer and number of years since stopping smoking, in men, based on available information from cohort studies

Reference	No. of years since stopping smoking	Mortality ratio (no. of observed deaths)
ACS 25-state study (Hammond, 1966)	1-19 cig./day	
	Current smokers	6.5 (80)
	<1	7.2 (3)
	1-4	4.6 (5)
	5-9	1.0 (1)
	10+	0.4 (1)
	Nonsmokers	1.0 (32)
	20+ cig./day	
	Current smokers	13.7 (351)
	<1	19.1 (33)
	1-4	12.0 (33)
	5-9	7.2 (32)
	10+	1.1 (5)
	Nonsmokers	1.0 (32)
Swedish study (Cederlöf et al., 1975)	<10	6.1 (12)
	>10	1.1 (3)
	Nonsmokers	1.0 (7)
British doctors study (Doll and Peto, 1976)	Current smokers	15.8 (123)
	1-4	16.0 (15)
	5-9	5.9 (12)
	10-14	5.3 (9)
	15+	2.0 (7)
	Nonsmokers	1.0 (7)
Rogot and Murray (1980)	Current smokers	11.3 (2,609)
	<5	18.8 (47)
	5-9	~7.5 (86)
	10-14	~5.0 (100)
	15-19	~5.0 (115)
	20+	2.1 (123)
	Nonsmokers	1.0 NA

NA = not available.

Source: IARC, 1986.

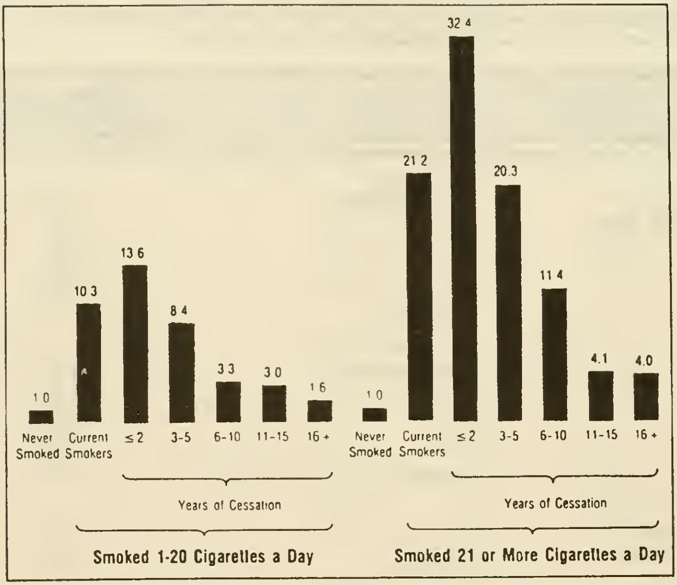


Figure 4-3. Relative risk of lung cancer in ex-smokers, by number of years quit, women, Cancer Prevention Study II.

Source: Garfinkel and Silverberg, 1991.

Table 4-7. Relative risks of lung cancer in some large cohort studies among men smoking cigarettes and other types of tobacco

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
ACS 9-state study[1]	Never smoked	1.0	12.8	15
	Occasionally only	1.5	19.2	8
	Cigarettes only	9.9	27.2	249
	Cigars only	1.0	13.1	7
	Pipes only	3.0	38.5	18
	Cigarettes + other	7.6	97.7	148
	Cigars + pipes	0.6	7.3	3
Canadian veterans study	Nonsmokers	1.0		7
	Cigarettes only	14.9		325
	Cigars only	2.9		2
	Pipe only	4.4		18
	Ex-smokers	6.1		18
ACS 25-state study[1]	Never smoked	1.0	12	49
	Cigarettes only	9.2	111	719
	Cigars only	1.9	22	23
	Pipes only	2.2	27	21
	Cigarettes + other	7.4	89	336
	Cigars + pipes	0.9	11	11
Swedish study[1]	Nonsmokers	1.0		7
	Cigarettes only	7.0		28
	Cigarettes + pipe	10.9		27
	Pipe only	7.1		31
	Cigars only	9.2		6
	Ex-smokers	6.1		12

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Table 4-7. (continued)

Study	Smoking category	Relative risk	Death rate per 100,000	No. of cases
British doctors study	Nonsmokers	1.0	10	
	Current smokers	10.4	104	
	Cigarettes only	14.0	140	
	Pipes and/or cigars only	5.8	58	
	Cigarettes + other	8.2	82	
	Ex-smokers	4.3	43	
U.S. veterans study[1]	Nonsmokers	1.0		2,609
	Cigarettes	11.3		1,095
	Cigarettes only	12.1		41
	Cigars only	1.7		32
	Pipes only	2.1		517
	Ex-cigarette smokers	4.0		
Norwegian study[1]	Nonsmokers	1.0		7
	Cigarettes	9.7		88
	Cigarettes only	9.5		70
	Pipes or cigars only	2.6		12
	Ex-smokers	2.8		11

[1] Figures given in original report.

Source: IARC, 1986.

Table 4-8. Age-adjusted lung cancer mortality ratios for males and females, by tar and nicotine (T/N) in cigarettes smoked

	Males	Females
High T/N[1]	1.00	1.00
Medium T/N	0.95	0.79
Low T/N	0.81	0.60

[1] The mortality rate for the category with highest risk was made 1.00 so that the relative reductions in risk with the use of lower T/N cigarettes could be visualized.

Source: U.S. DHHS, 1982.

Table 4-9. Relative risk for lung cancer by type of cigarette smoked (filter vs. nonfilter), in men, based on cohort and case-control studies

Reference	Type of study	Relative risk
Hawthorne and Fry (1978)	Cohort	0.8
Rimington (1981)	Cohort	0.7
Bross and Gibson (1968)	Case-control	0.6
Wynder et al. (1970)	Case-control	0.6
Dean et al. (1977)	Case-control	0.5

Source: IARC, 1986.

Table 4-10. Main results of studies dealing with the relationship between smoking and different histological types of lung cancer

Reference	Histological type	Results						Comments	
Doll et al. (1957)		Sex	No. of cases	Relative risk				Nonsmokers, 1.0 (RR)	No. observed
				Amount of tobacco smoked (g)					
				<5	5-14	15-24	25+		
	Kreyberg I	M	829	4.7	10.6	14.3	25.4		3
		F	32	1.0	1.7	8.3			16
	Kreyberg II	M	38	0.5	0.8	1.2	1.1		2
		F	8	1.1	2.3	4.1			5
Hammond and Horn (1958b)		Relative risk no. of packs/day						Nonsmokers, 1.0. Only regular smokers considered	
		<½	½-1	1+					
	Adenocarcinoma	2.0	2.5	7.0					
	Other types	16.3	25.5	88.0					
Doll and Hill (1964a)		Death rate per 1,000 Amount of tobacco smoked (g)						Men only	
		Ex-smokers	1-14	15-24	25+				
	Squamous-cell carcinoma	0.09	0.22	0.33	0.45				
	Small-cell and anaplastic carcinoma	0.05	0.10	0.20	0.38				
	Adenocarcinoma	0.03	0.03	0.12	0.07				

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Table 4-10. (continued)

Reference	Histological type	Results					Comments
Haenszel and Taeuber (1964)		Standardized mortality ratio					Women only; standardized mortality ratio; total group, 1.00
		Never-smokers	Ex-Smokers	Occasional cigarette smokers	Regular cigarette smokers		
					<1 pack/day	>1 pack/day	
	Adenocarcinoma	0.78	0.35	2.46	1.17	7.50	
	Squamous-cell and undifferentiated carcinoma	0.59	0.52	1.15	2.19	8.58	
Hanbury (1964)		No. of cases (%)					Women only
		"Heavy" and "medium" smokers	Nonsmokers and "remainder"				
	Small-cell carcinoma	18 (47)	21 (34)				
	Undifferentiated carcinoma	9 (24)	14 (23)				
	Squamous-cell carcinoma	9 (24)	12 (19)				
	Adenocarcinoma	2 (5)	15 (24)				

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Table 4-10. (continued)

Reference	Histological type		Results										Comments
Vincent et al. (1965)			Number of cigarettes smoked/day										Women only
		Total no. of cases	None		1-20		21-40		41+		Unknown		
			No.	%	No.	%	No.	%	No.	%	No.	%	
	Squamous-cell carcinoma	19	10	53	3	16	2	10	2	10	2	10	
	Small-cell carcinoma	17	2	12	7	41	6	35	2	12	0	0	
	Adenocarcinoma	64	51	80	6	9	4	6	0	0	3	5	
	Undifferentiated	22	12	54	4	18	6	27	0	0	0	0	
	Others	41	32	78	8	20	1	2	0	0	0	0	
		163	107	66	28	17	19	12	4	2	5	3	

Wynder et al. (1970)		Sex	No. (%)		Heavy = 41+ cigarettes/day
			Cigarette smokers	Heavy smokers	
	Kreyberg I	M	191 (91.0)	59 (29.9)	
		F	24 (80.0)	3 (12.0)	
	Kreyberg II	M	61 (82.4)	9 (14.1)	
		F	21 (58.3)	1 (4.8)	
	Controls	M	199 (47.4)	26 (9.8)	
		F	53 (40.2)	3 (5.4)	

(continued on the following page)

Table 4-10. (continued)

Reference	Histological type	Results					Comments
Deaner and Trummer (1970)		Pack-years	Number of tumors	Smokers			
	Undifferentiated carcinoma	40	40	40 (100%)			
	Adenocarcinoma	12	19	13 (68%)			
	Squamous-cell carcinoma	52	9	9 (100%)			
Weiss et al. (1972)		Death rate per 1,000 man-years of observation (adjusted for age and race) No. of cigarettes/day					
		1-10	10-19	20+			
	Squamous-cell carcinoma						
	Well differentiated	-	0.8	2.1			
	Poorly differentiated	0.7	0.4	1.0			
	Small-cell carcinoma	-	0.3	0.7			
	Adenocarcinoma	-	0.6	1.0			
Vincent et al. (1977)		No. of cigarettes smoked/day					
		0	1-20	21-40	41+	Other	
	Squamous-cell carcinoma	14	219	110	120	16	
	Adenocarcinoma	28	101	66	53	7	
	Small-cell carcinoma	4	103	62	56	6	
	Large-cell carcinoma	2	40	32	33	0	
	Bronchiolo-alveolar carcinoma	6	20	9	6	0	
	Mixed	0	9	5	5	0	
	Other	6	30	19	17	4	

(continued on the following page)

Table 4-10. (continued)

Reference	Histological type	Results								Comments
Chan et al. (1979)		Smoking category (kg tobacco smoked during lifetime)								Women only
			<100		100-199		>200			
		Non-smokers	Manufactured	All	Manufactured	All	Manufactured	All		
	Squamous-cell and small-cell carcinomas	1.0	3.6	3.4	3.7	4.2	2.6	4.1		
	Adenocarcinoma	1.0	1.9	1.4	1.4	1.8	1.6	1.7		
Joly et al. (1983)		Relative risk by duration of smoking (years)								Nonsmokers, 1.0
		Men				Women				
		1-29	30-39	40-49	50+	1-29	30-39	40-49	50+	
	Squamous-cell carcinoma	15.0	15.9	39.5	42.2	4.4	9.4	31.4	51.9	
	Adenocarcinoma	2.0	3.2	5.3	5.7	2.1	2.7	4.7	4.0	
	Undifferentiated carcinoma	26.0	26.4	40.7	50.0	3.9	15.6	20.6	28.3	
	Poorly differentiated carcinoma	6.4	7.7	10.8	10.2	3.2	7.8	5.6	13.1	

Source: IARC, 1986.

estimates, particularly in women. There are four major histological types of lung cancer: squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma, and large-cell undifferentiated carcinoma. Sometimes two broad categories--Kreyberg Group I, containing squamous-cell and small-cell carcinomas, and Kreyberg Group II, containing all other epithelial lung cancers, including adenocarcinomas and large-cell undifferentiated carcinomas--are used for classification. The majority of the studies demonstrate an increase in the risk for lung cancer with increasing amount smoked for all four major histological groups in both males and females. The slope of the gradient for adenocarcinomas, however, is shallower than the slopes for the other types.

4.2.4. Proportion of Risk Attributable to Active Smoking

Table 4-11 presents data on the proportion of lung cancer deaths attributable to smoking in various countries. Differences by sex and between countries largely correlate with differences in the proportion of smokers within these populations and the duration and intensity of cigarette usage. In the early 1960s, 50% of U.S. men and 30% of U.S. women smoked, although these proportions have been declining in recent years (Garfinkel and Silverberg, 1991).

In the United States, deaths from lung cancer currently represent one-quarter of all cancer deaths. The American Cancer Society predicted there would be 143,000 lung cancer deaths in 1991 (Garfinkel and Silverberg, 1991). Over 85% of this lung cancer mortality is estimated to be attributable to tobacco smoking. In other words, the overwhelming majority of lung cancer deaths, which are a significant portion of all cancer deaths, result from smoking. The strong association between smoking and lung cancer and the dose-response relationships, with effects observable at low doses and no evidence of a threshold, make it highly plausible that passive smoking also causes lung cancer in humans.

4.3. LIFETIME ANIMAL STUDIES

The human evidence for the carcinogenicity of tobacco smoke is corroborated in experimental animal bioassays. The main animal evidence is obtained from inhalation studies in the hamster, intrapulmonary implantations in the rat, and skin painting in the mouse. There are no lifetime animal inhalation studies of ETS; however, the carcinogenicity of SS condensates has been demonstrated in intrapulmonary implantations and skin painting experiments.

Negative responses in short-term animal studies (e.g., 60 to 90 days) are not reliable indicators of the carcinogenic potential of a compound because of the long latency period for cancer development. Long-term animal studies at or near the maximum tolerated dose level are used to ensure an adequate power for the detection of carcinogenic activity (U.S. EPA, 1986a).

Table 4-11. Lung cancer deaths attributable to tobacco smoking in certain countries

Country	Year	No. of deaths[1]	Expected deaths in nonsmokers[2]	Crude rate in persons aged 35+ Observed	Crude rate in persons aged 35+ In nonsmokers	AC[3]	AP[4]
Canada							
Men	1978	6,435	556	142.8	11.8	5,762	0.9
Women	1978	1,681	487	34.0	9.9	1,194	0.71
England and Wales							
Men	1981	26,297	1,576	228.5	13.3	24,720	0.94
Women	1981	8,430	1,663	63.3	12.4	6,767	0.80
Japan							
Men	1981	16,638	2,868	64.8	10.7	13,184	0.83
Women	1981	6,161	2,593	21.0	8.9	3,568	0.58
Sweden							
Men	1981	1,777	301	85.0	14.0	1,476	0.83
Women	1981	654	281	28.0	12.3	373	0.57
USA							
Men	1979	72,803	5,778	166.7	12.7	67,024	0.92
Women	1979	25,648	5,736	50.0	11.1	19,912	0.78

[1] From the Global Epidemiological Surveillance and Health Situation Assessment data bank of WHO.

[2] Calculated by IARC, 1986. Slightly overestimates number of expected deaths.

[3] AC, number of cases attributable to smoking.

[4] AP, proportion of cases attributable to smoking.

Source: IARC, 1986.

4.3.1. Inhalation Studies

Although evidence of the carcinogenicity of cigarette smoke originated in humans, attempts were made to develop an inhalation model for smoking in experimental animals in order to study the carcinogenicity of various tobacco products. Such inhalation studies are difficult to conduct, however, because laboratory animals are reluctant to inhale cigarette smoke and will adopt shallow breathing patterns in response to aerosols and irritants. Furthermore, rodents are obligatory nose-breathers, and the anatomy and physiology of the respiratory tract and the biochemistry of the lung differ between rodents and humans. Because of these distinctions, laboratory animals and humans are likely to have different deposition and exposure patterns for the various cigarette smoke components in the respiratory system. For example, rodents have extensive and complex nasal turbinates where significant particle deposition could occur, decreasing exposure to the lung.

The Syrian golden hamster has been the most useful animal inhalation model found so far for studying smoking-induced carcinogenesis. It is more tolerant of tobacco smoke than mice and rats and is relatively resistant to respiratory infections. The hamster also has a low background incidence of spontaneous pulmonary tumors and is, in fact, refractory to the induction of lung cancers by known carcinogenic agents. The inhalation of tobacco smoke by the hamster does, however, induce carcinomas of the larynx. In one study (Dontenwill et al., 1973), three groups of 80 male and 80 female Syrian golden hamsters were exposed for 10 minutes to air-diluted cigarette smoke (1:15) once, twice, or three times daily, 5 days per week, for their lifetimes. Preinvasive carcinomas of the upper larynx were detected in 11.3%, 30%, and 30.6% of the animals, respectively, and invasive carcinomas were found in 0.6%, 10.6%, and 6.9%, respectively. No laryngeal tumors were observed in control animals. In another experiment, exposure for 59 to 80 weeks to an 11% or 22% cigarette smoke aerosol twice daily for 12 minutes resulted in laryngeal carcinomas in 3 of 44 and 27 of 57 animals, respectively, providing some evidence of a dose-response relationship for the induction of carcinoma of the larynx by cigarette smoke (Bernfeld et al., 1979). Bernfeld et al. suggest that the greater deposition of tar per unit of surface area in the larynx compared to the lung may explain the high yield of laryngeal cancers and lack of lung tumors in this animal model.

4.3.2. Intrapulmonary Implantations of Cigarette Smoke Condensates

Because of the difficulties with inhalation studies of cigarette smoke, some in vivo studies examine the carcinogenicity of cigarette smoke condensate (CSC) collected from smoking machines. CSC assays may not, however, reveal all of the carcinogenic activity of actual cigarette smoke, because these condensates lack most of the volatile and semivolatile components of whole smoke. In lifetime rat studies, intrapulmonary implants of MS condensate in a lipid vehicle cause a dose-dependent increase in the incidence of lung carcinomas (Stanton et al., 1972; Dagle et al., 1978).

SS condensates have also demonstrated carcinogenicity when implanted into rat lungs (Grimmer et al., 1988). SS emitted by a smoking machine was separated into condensate fractions containing the semivolatiles, the polycyclic aromatic hydrocarbon (PAH)-free particulates and the PAHs with two or three rings, or the PAHs with four or more rings. These fractions were implanted into female Osborne-Mendel rats, following the procedure of Stanton et al. (1972), at a dose level of one cigarette per animal. At the end of the lifetime study, none of the 35 rats in each of the untreated control, vehicle control, or semivolatile-exposed groups had lung carcinomas. In the group exposed to the fraction containing PAH-free particulates and PAHs with 2 or 3 rings, there was 1 lung carcinoma in 35 animals. In the group exposed to the fraction comprising PAHs with 4 or more rings, there were 5 lung carcinomas in 35 rats. An additional group that was exposed to a dose of 0.03 mg benzo[a]pyrene (BaP) per rat exhibited 3 lung carcinomas in 35 animals. The condensate fraction containing BaP and the other PAHs with four or more rings from the SS generated by a single cigarette contains about 100 ng of BaP. Assuming a linear, nonsynergistic dose-response relationship, this would suggest that less than 1% of the total carcinogenicity of that condensate fraction can be attributed to the BaP present in the smoke.

4.3.3. Mouse Skin Painting of Cigarette Smoke Condensates

In addition, numerous studies have shown that when MS condensate suspended in acetone is chronically applied to mouse skin, significant numbers of the mice develop papillomas or carcinomas at the site of application (e.g., Wynder et al., 1957; Davies and Day, 1969). Mouse skin studies have also demonstrated that MS condensate has both tumor-initiating and tumor-promoting capabilities (Hoffman and Wynder, 1971).

One mouse skin painting study examined the carcinogenicity of SS condensate (Wynder and Hoffman, 1967). Cigarette tar from SS deposited on the funnel of a smoking machine was suspended in acetone and administered to mouse skin. Fourteen of thirty mice developed skin papillomas, and 3 of 30 developed carcinomas. In a parallel assay in the same study, a suspension of MS condensate applied to deliver a comparable amount of condensate to the skin of 100 mice yielded benign skin tumors in 24 and malignant tumors in 6 of the mice. This suggests that the condensate of SS has greater mouse skin tumorigenicity per unit weight than that of MS.

4.4. GENOTOXICITY

Supportive evidence for the carcinogenicity of tobacco smoke is provided by the demonstration of genotoxicity in numerous short-term assays. Extensive reviews of these studies can be found in IARC (1986) and DeMarini (1983); only the highlights are presented here. A few studies deal with whole smoke, but most examine CSC. Tobacco smoke is genotoxic in virtually every in vitro system tested, providing overwhelming supportive evidence for its carcinogenic potential.

In *Salmonella typhimurium*, for example, Basrur et al. (1978) found that both whole MS and MS condensates from various types of tobacco were mutagenic in the presence of a metabolic activating system. SS (Ong et al., 1984) and extracts of ETS collected from indoor air (Löfroth et al., 1983; Alfheim and Ramdahl, 1984; Lewtas et al., 1987; Ling et al., 1987; Löfroth et al., 1988) also exhibit mutagenic activity in this bacterium. Claxton et al. (1989) found that SS accounted for approximately 60% of the total *S. typhimurium* mutagenicity per cigarette--40% from the SS particulates and 20% from the semivolatiles. The highly volatile fraction, from either MS or SS, was not mutagenic.

Similarly, cigarette smoke produced mitotic gene conversion, reverse mutation, and reciprocal mitotic recombination in fungi (Gairola, 1982). In addition, CSC's induce mutations, sister chromatid exchanges, and cell transformation in various mammalian cells in culture. Putnam et al. (1985) demonstrated dose-dependent increases in sister chromatid exchange frequencies in bone-marrow cells of mice exposed to cigarette smoke for 2 weeks.

4.5. SUMMARY AND CONCLUSIONS

Lung cancer mortality rates have increased dramatically over the past 60 years in males, and, more recently, in females, with increasing cigarette consumption. High relative risks for lung cancer, associated with the number of cigarettes smoked per day, have been demonstrated in countless studies, with no evidence of a threshold level of exposure. Active smoking induces all four major histological types of human lung cancer--squamous-cell carcinomas, small-cell carcinomas, large-cell carcinomas, and adenocarcinomas--all in a dose-related manner. Dose-response relationships have also been established with respect to duration of smoking. Furthermore, lung cancer risk increases with the younger the age at initiation of smoking and decreases with the longer the time since cessation of smoking. These latter trends, coupled with evidence from mouse skin painting studies, suggest that tobacco smoke has both tumor-initiating and tumor-promoting capabilities.

Inhalation studies in hamsters confirm that MS is carcinogenic to the respiratory tract. In addition, mouse skin painting experiments and intrapulmonary implantations in rats have demonstrated the carcinogenicity of condensates from both MS and SS (the primary component of ETS), with SS condensate having a greater potency than MS condensate in mouse skin painting studies. Numerous genotoxicity tests contribute supporting evidence for the carcinogenic potential of MS and SS smoke and smoke condensates. The mutagenicity of ETS and its extracts has also been established. One study found that SS accounted for 60% of the total mutagenicity per cigarette.

As discussed in Chapter 3, MS and ETS are qualitatively similar in composition, and both contain numerous known or suspected human carcinogens. ETS constituents include essentially all of the same carcinogens found in MS, and many of these appear in greater amounts in SS, and hence, in ETS, than in MS, per unit of tobacco burned. This quantitative comparison is consistent with the observation noted above that SS condensates apparently have even greater carcinogenic potential than MS condensates.

The unequivocal causal association between tobacco smoking and lung cancer in humans with dose-response relationships extending down to the lowest exposure categories, as well as the corroborative evidence of the carcinogenicity of both MS and ETS provided by animal bioassays and in vitro studies and the chemical similarity between MS and ETS (Chapter 3), clearly establish the plausibility that ETS is also a human lung carcinogen. In addition, biomarker studies verify that passive smoking results in detectable uptake of tobacco smoke constituents by nonsmokers, affirming that ETS exposure is a public health concern (Chapter 3).

In fact, these observations are sufficient in their own right to establish the carcinogenicity of ETS to humans. According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria (that) must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

Given the strong dose-related associations, with high relative risks consistently observed across numerous independent studies from several countries, and the biological plausibility provided by ancillary evidence of the genotoxicity and animal carcinogenicity of MS and by knowledge of the existence of many specific carcinogenic components within MS, confounding, bias, and chance can all be ruled out as possible explanations for the observed association between active smoking and lung cancer. Therefore, under the EPA carcinogen classification system, MS would be categorized as a Group A (known human) carcinogen. Furthermore, the extensive chemical and toxicological similarities between SS and MS, detailed in Sections 3.2, 4.3, and 4.4, strongly infer that SS is also capable of causing lung cancer in humans, as was documented for MS in Section 4.2. Thus, under EPA's carcinogen classification system, SS also belongs in Group A. Finally, because ETS is composed of SS and exhaled MS, and because ETS is known to be inhaled and absorbed into the body (Section 3.3.2), ETS would similarly be categorized as a Group A carcinogen.

In addition, there exists a vast body of epidemiologic data dealing specifically with lung cancer and exposure to ETS. These data should also be examined in the interest of weighing all the available evidence, as recommended by EPA's carcinogen risk assessment guidelines (U.S. EPA, 1986a), both for hazard identification and exposure-response assessment. The rapid dilution of both SS and exhaled MS into the environment and changing phase distributions of ETS components over time raise some questions about the carcinogenic potential of ETS under actual environmental exposure conditions. Furthermore, while MS and ETS may be qualitatively comparable, active smoking data do not constitute a good basis for quantitative estimation of the health effects of passive smoking because the relative uptake and deposition between active and passive smokers of the agent(s) responsible for these effects are not known (see Chapters 2 and 6). Provided the epidemiologic studies are of sufficient power and adequate study design, this database can offer unique information on the actual lung cancer risk to nonsmokers from exposure to true ambient levels of ETS. The epidemiologic evidence for the human lung carcinogenicity associated specifically with ETS is the subject of Chapter 5. These epidemiologic data are then used as the basis for the calculation of population risk estimates for lung cancer from passive smoking in Chapter 6.

5. HAZARD IDENTIFICATION II: INTERPRETATION OF EPIDEMIOLOGIC STUDIES ON ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

5.1. INTRODUCTION

The Centers for Disease Control attributed 434,000 U.S. deaths in 1988 to smoking (CDC, 1991a). Major disease groups related to smoking mortality include lung cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke, with smoking accountable for an estimated 87%, 82%, 21%, and 18% of total deaths, respectively. Lung cancer alone accounted for about 25% to 30% of the total smoking mortality, with some 100,000 deaths. The age-standardized annual lung cancer mortality rates for 1985 are estimated at 12 per 100,000 for females and 15 per 100,000 for males who never smoked but 130 per 100,000 for female cigarette smokers and 268 per 100,000 for male cigarette smokers, a relative risk of 10.8 and 17.4, respectively (Garfinkel and Silverberg, 1991).

Chapter 4 discusses the biological plausibility that passive smoking also may be a risk factor for lung cancer because of the qualitative similarity of the chemical constituency of sidestream smoke, the principal source of environmental tobacco smoke (ETS), and mainstream smoke taken in during the act of "puffing" on a cigarette, and because of the apparent nonthreshold nature of the dose-response relationship observed between active smoking and lung cancer. Although the relative risk of lung cancer from passive smoking would undoubtedly be much smaller than that for active smoking, the ubiquity of ETS exposure (Chapter 3) makes potential health risks worth investigating.

This chapter analyzes the data from the large number of epidemiologic studies on ETS and lung cancer that contain data on the effects of ETS on never-smoking women. Although some of the studies involve male nonsmokers and former smokers of both sexes, the female never-smokers comprise the large majority of the database--more than 3,000 cases and 6,000 controls in the 27 case-control studies and almost 300,000 female never-smokers followed in the 4 cohort studies. Whenever study data are separated by sex and smoking status, women never-smoker results are used. The use of a more homogeneous group allows more confidence in the results of combined study analyses. All of the studies used provide data on adult home exposure to ETS. Some also provide information on childhood and/or workplace exposure, but there is far less information on these exposures; therefore, in order to develop one large database for analysis, only the female exposures from spousal smoking are considered. The exposure surrogate used is a report of the husband's smoking status. Wherever a measure of the amount of exposure to husband's smoking is available, additional analyses are performed to examine effects in the highest exposure groups (Section 5.3.3.2) and dose-response relationships (Section 5.3.3.3). Virtually all of the 31 studies available classify never-smoking women as "exposed" or "unexposed" to ETS based on self- or proxy-reported smoking in the subject's environment, usually according to whether or not a woman is married to a smoker. In addition, 17 studies provide sufficient information for highest exposure group and exposure-response analyses. Other analyses of the data include adjusting for the potential upward bias of smoker misclassification (Section 5.2.2); examining confounders, effect modifiers, and sources of potential bias (Section 5.4); and pooling qualitatively higher ranked studies (Section 5.5). It is hoped that by analyzing the data in several different ways, a clear picture will emerge (Section 5.6).

Throughout this chapter, one-tailed tests of significance ($p = 0.05$) are used, which increases the statistical ability (power) to detect an effect. The 90% confidence intervals used for the analyses performed are consistent with the use of the one-tailed test. The justification for this usage is based on the *a priori* hypothesis (from the plausibility of a lung cancer effect documented in Chapters 3 and 4) that a positive association exists between exposure to ETS and lung cancer.

Epidemiologic evidence of an association between passive smoking and lung cancer first appeared 10 years ago in a prospective cohort study in Japan (Hirayama, 1981a) and a case-control study in Greece (Trichopoulos et al., 1983). Both studies concluded that the lung cancer incidence and mortality in nonsmoking women was higher for women married to smokers than for those married to nonsmokers. Although there are other sources of exposure to ETS, particularly outside the home, the assumption is that women married to smokers are exposed to more tobacco smoke, on average, than women married to nonsmokers. These two studies, particularly the cohort study from Japan, evoked considerable critical response. They also aroused the interest of public health epidemiologists, who initiated additional studies.

At the request of two Federal agencies--the U.S. Environmental Protection Agency (Office of Air and Radiation) and the U.S. Department of Health and Human Services (Office of Smoking and Health)--the National Research Council (NRC) formed a committee on passive smoking to evaluate the methods for assessing exposure to ETS and to review the literature on the health consequences. The committee's report (NRC, 1986) addresses the issue of lung cancer risk in considerable detail and includes summary analyses of the evidence from 10 case-control and 3 cohort (prospective) studies. It concludes, "Considering the evidence as a whole, exposure to ETS increases the incidence of lung cancer in nonsmokers."

The NRC committee was particularly concerned about the potential bias in the study results caused by the fact that current and former smokers may have incorrectly reported themselves as lifelong nonsmokers (never-smokers). Using reasonable assumptions for misreported smoking habits, the committee determined that a plausible range for the true relative risk is 1.15 to 1.35, with 1.25 the most likely value. When these relative risks also are corrected for background exposure to ETS to make the risk relative to a baseline of zero ETS exposure, the resultant estimate is 1.42, with a plausible range of 1.24 to 1.61.

Two other major reports on passive smoking have appeared: the Surgeon General's report on the health consequences of passive smoking (U.S. DHHS, 1986) and the report on methods of analysis and exposure measurement related to passive smoking by the International Agency for Research on Cancer (IARC, 1987a). The Surgeon General's report concludes:

> The absence of a threshold for respiratory carcinogenesis in active smoking, the presence of the same carcinogens in mainstream and sidestream smoke, the demonstrated uptake of tobacco smoke constituents by involuntary smokers, and the demonstration of an increased lung cancer risk in some populations with exposures to ETS lead to the conclusion that involuntary smoking is a cause of lung cancer.

The IARC committee emphasized issues related to the physicochemical properties of ETS, the toxicological basis for lung cancer, and methods of assessing and monitoring exposure to ETS. Included in the 1987 IARC report is a citation from the summary statement on passive smoking of a previous IARC report that the epidemiologic evidence available at that time (1985) was compatible with either the presence or absence of lung cancer risk. Based on other considerations related to biological plausibility, however, it concludes that passive smoking gives rise to some risk of cancer. Specifically, the report (IARC, 1986) states:

> Knowledge of the nature of sidestream and mainstream smoke, of the materials absorbed during "passive smoking," and of the quantitative relationships between dose and effect that are commonly observed from exposure to carcinogens . . . leads to the conclusion that passive smoking gives rise to some risk of cancer.

In the years since those reports, the number of studies available for analysis has more than doubled. There are now 31 epidemiologic studies available from eight different countries, listed in Table 5-1. Twenty-seven studies employ case-control designs, denoted by the first four letters of the first author's name for convenient reference, and four are prospective cohort studies, distinguished by the designation "(Coh)." Six case-control studies, FONT (USA), JANE (USA), KALA (Greece), LIU (China), SOBU (Japan), and WUWI (China), have been published as recently as 1990. The small cohort study from Scotland (Gillis et al., 1984) has been updated and is now included under the name HOLE(Coh); another small cohort study on Seventh-Day Adventists in the United States, an unpublished dissertation, is included as BUTL(Coh). The abstracts for a second case-control study by Kabat and Wynder and a new one by Stockwell and colleagues are included in Section A.4, but insufficient information is available to include their results.

Table 5-1. Epidemiologic studies on ETS and lung cancer in this report and tier ranking

Study	Tier[1]	Country	Within country	References
AKIB	2	Japan	Hiroshima	Akiba et al. (1986)
BROW	3	United States	Colorado	Brownson et al. (1987)
BUFF	3	United States	Texas	Buffler et al. (1984)
CHAN	4	Hong Kong		Chan and Fung (1982)
CORR	2	United States	Louisiana	Correa et al. (1983)
FONT	1	United States	Five metro areas	Fontham et al. (1991)
GAO	3	China	Shanghai	Gao et al. (1987)
GARF	2	United States	New Jersey, Ohio	Garfinkel et al. (1985)
GENG	4	China	Tianjin	Geng et al. (1988)
HUMB	2	United States	New Mexico	Humble et al. (1987)
INOU	4	Japan	Kanajawa	Inoue and Hirayama (1988)
JANE	2	United States	New York	Janerich et al. (1990)
KABA	2	United States	New York	Kabat and Wynder (1984)
KALA	1	Greece	Athens	Kalandidi et al. (1990)
KATA[2]		Japan		Katada et al. (1988)
KOO	1	Hong Kong		Koo et al. (1987)
LAMT	2	Hong Kong		Lam et al. (1987)
LAMW	3	Hong Kong		Lam (1985)
LEE	2	England		Lee et al. (1986)
LIU	4	China	Xuanwei	Liu et al. (1991)
PERS	1	Sweden		Pershagen et al. (1987)
SHIM	2	Japan	Nagoya	Shimizu et al. (1988)
SOBU	2	Japan	Osaka	Sobue (1990)
SVEN	2	Sweden	Stockholm	Svenson et al. (1989)

(continued on the following page)

Table 5-1. (continued)

Study	Tier	Country	Within country	References
TRIC	3	Greece	Athens	Trichopoulos et al. (1981, 1983)
WU	2	United States	California	Wu et al. (1985)
WUWI	4	China		Wu-Williams and Samet (1990)
BUTL(Coh)	2	United States	California	Butler (1988)
GARF(Coh)	3	United States		Garfinkel (1981)
HIRA(Coh)	2	Japan		Hirayama (1984)
HOLE(Coh)	1	Scotland	Paisley Renfrew	Hole et al. (1989)

[1] Tier rankings refer to this report's ratings of studies for utility of studying the association of ETS and lung cancer, where "1" is highest (see Section 5.5 and Section A.3).
[2] KATA has no tier number because the odds ratio cannot be calculated.

Because of coincidental timing, the 1986 reports of the Surgeon General and the NRC review approximately the same epidemiologic studies. More specifically, the NRC report includes nine of the studies shown in Table 5-1: AKIB, CHAN, CORR, GARF, KABA, KOO, LEE, PERS, and TRIC; WU was available but not included because the crude data were not reported. (Crude data consist of the number of exposed and unexposed subjects among lung cancer cases and controls, where a subject is typically classified as exposed to ETS if married to a smoker.) The NRC also excluded an earlier version of the KOO study and the studies by Knoth et al. (1983) (no reference population was given), Miller (1984) (did not report on lung cancers separately), and Sandler et al. (1985) (included very few lung cancers). Aside from WU, these studies also are omitted from this report for the same reasons.

Tables 5-2 and 5-3 provide an overview of some descriptive features of the individual ETS studies included in this report. The studies are grouped by country in Table 5-2, which indicates the time period of data collection in each study, sample size, and prevalence of ETS exposure for each study. The geographical distribution of the current epidemiologic evidence is diverse. By country, the number of studies and its percentage of the total number of studies over all countries is as follows: China (4, 13%), England (1, 3%), Greece (2, 6%), Hong Kong (4, 13%), Japan (6, 19%), Scotland (1, 3%), Sweden (2, 6%), and United States (11, 35%). (One of the

Table 5-2. Studies by location, time, size, and ETS exposure

Country	Study	Accrual[1] period	Size[2]		ETS exposure (%)[3]	
			Cases	Controls	Cases	Controls
Greece	KALA	1987-89	90	116	71	60
Greece	TRIC	1978-80	40	149	73	52
Hong Kong	CHAN	1976-77	84	139	60	53
Hong Kong	KOO	1981-83	86	136	59	49
Hong Kong	LAMT	1983-86	199	335	58	45
Hong Kong	LAMW	1981-84	60[4]	144[4]	62[4]	44[4]
Japan	AKIB	1971-80	94	270	78	70
Japan	HIRA(Coh)	1965-81	— 91,540 —		— 76 —	
Japan	INOU	1973-83	22	47	82	64
Japan	SHIM	1982-85	90	163	58	56
Japan	SOBU	1986-88	144	731	56	54
USA	BROW	1979-82	19	47	21	15
USA	BUFF	1976-80	41	196	80	84
USA	BUTL(Coh)	1976-82	— 9,207[5] —		— 34[5] —	
USA	CORR	1979-82	22	133	64	46
USA	FONT	1985-88	420	780[6]	70	63[6]
USA	GARF	1971-81	134	402	67	61
USA	GARF(Coh)	1959-72	— 176,739 —		— 72 —	
USA	HUMB	1980-84	20	162	75	56
USA	JANE	1982-84	191	191	*[7]	60[7]
USA	KABA	1961-80	24	25	54	60
USA	WU	1981-82	29[8]	62[8]	*	*
W. Europe						
Scotland	HOLE(Coh)	1972-85	— 1,784 —		— 73 —	
England	LEE	1979-82	32	66	69	68

(continued on the following page)

Table 5-2. (continued)

Country	Study	Accrual[1] period	Size[2] Cases	Size[2] Controls	ETS exposure (%)[3] Cases	ETS exposure (%)[3] Controls
W. Europe (continued)						
Sweden	PERS	1961-80	67	*	49	*
Sweden	SVEN	1983-85	34	174	71	66
China	GAO	1984-86	246	375	77	74
China	GENG	1983	54	93	63	44
China	LIU	1985-86	54	202	83	87
China	WUWI	1985-87	417	602	49	55

[1] Time during which cases occurred.

[2] Number of subjects included in ETS analyses; where numbers differ for spousal smoking and other exposures, those for spousal smoking are given.

[3] Spousal smoking unless otherwise noted.

[4] Adenocarcinoma only. Data for all cell types were available only for general passive smoke exposure, which showed 77% of 75 cases and 56% of 144 controls exposed.

[5] Figure pertains to "spouse pairs" cohort, which is of principal interest regarding ETS; a subgroup of this cohort comprised the "ASHMOG" cohort.

[6] Figure is for population controls; study also included 351 colon cancer controls (66% exposed).

[7] ORs but no exposure prevalences are presented for spousal smoking in the source. The value shown for controls is taken from KABA, as closest to JANE in time and location; no exposure percentage is assumed for cases.

[8] Adenocarcinoma only. Analyses for other cell types included smokers while adjusting for smoking status.

*Data not available.

Table 5-3. Case-control studies of ETS: characteristics

	Percentage proxy response[1]		Female age[2]				
Study	Ca	Co	Ca	Co	Source of controls	Matched variables	ETS sample matched
AKIB	90	88	70.2 35-95	* *	Atomic bomb survivor population	Age, sex, residence, vital status, med. subject[3]	No
BROW	69	39	66.3	68.2	Cancer cases[4]	Age, sex	No[5]
BUFF	82	76	30-79	30-79	Cancer cases[6]	Age, sex	No[5]
CHAN	*	*	39-70	39-70	Orthopedic patients	Matched but variables unspecified	No[5]
CORR	*	*	*	*	Hospital patients[7]	Age (± 5), sex, race	No[5]
FONT	34	0-10[8]	20-79	20-79	Cancer cases; general population	Age, (for cancer controls) race	Yes
GAO	0	*	35-69	35-69	General population	Age (± 5)	No[5]
GARF	88	*	≥40	≥40	Cancer cases[9]	Age (± 5), hospital	Yes
GENG	0	0	≤65	≤65	*	Age (± 2), sex, race, marital status	No[5]
HUMB	*	*	≤85	≤85	General population	Age (± 10), sex, ethnicity	No[5]
INOU	*	*	*	*	Cerebrovascular disease deaths	Age, year of death (± 2.5), district	No[5]
JANE	33[10]	33[10]	67.1[10]	68.1[10]	New York State Dept. of Motor Vehicles	Age, sex, county, smoking history	Yes

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Table 5-3. (continued)

	Percentage proxy response[1]		Female age[2]				
Study	Ca	Co	Ca	Co	Source of controls	Matched variables	ETS sample matched
KABA	0	0	61.6	53.9	Patients[11]	Age (± 5), sex, race, hospital	Yes
KALA	0	0	≥35	≥35	Orthopedic patients	Sex	Yes
KATA	0	0	67.8	*	Noncancer patients	Age (± 2), sex	Yes
KOO	0	0	*	*	"Healthy"[12]	Age (± 5), residence, housing	No[5]
LAMT	0	0	*	*	"Healthy"[13]	Age (± 5), residence	No[5]
LAMW	*	*	67.5	66	Hospitalized orthopedic patients	Age, socio-economic status, residence[14]	No[5]
LEE	38[15]	38	35-74	35-74	Patients[16]	Age, sex, hospital location, time of interview	No[5,17]
LIU	0	0	52	52	General population?	Age (± 2), sex, village	Yes
PERS	*[18]	*	*[19]	*	*[20]	Age (± 1), sex	Yes
SHIM	0	0	59 35-81	58 35-81	Patients[21]	Age (± 1), hospital, admission date	Yes
SOBU	0	0	60	56	Patients	None	No
SVEN	0	0	66.3		General population	Age	No[5]

(continued on the following page)

Table 5-3. (continued)

Study	Percentage proxy response[1]		Female age[2]		Source of controls	Matched variables	ETS sample matched
	Ca	Co	Ca	Co			
TRIC	0	0	62.8	62.3	Hospitalized orthopedic patients	Age, occupation, education[14]	No[5]
WU	0	0	<76	<76	Neighborhood[13]	Age (± 5), sex, race	No[5]
WUWI	0	0	55.9[22]	55.4[22]	General population	Sex, age[23]	No[5]

[1] "Ca" and "Co" stand for "cases" and "controls," respectively.
[2] Single values are the average or median. Paired values are the range.
[3] Participation in RERF biennial medical examination program.
[4] Persons with cancers of bone marrow or colon in Colorado Control Cancer Registry.
[5] Not matched on personal smoking status (e.g., smoker/nonsmoker).
[6] Population-based and decedent comparison subjects selected from state and Federal records.
[7] Assorted ailments.
[8] 0% for general population and 10% for colon cancer controls.
[9] Colorectal cancer.
[10] Includes males and females and long-term ex-smokers.
[11] Diseases not related to smoking.
[12] Selected from a healthy population.
[13] Living in neighborhood of matched case.
[14] "Similar" but not actually matched.
[15] Applies only to the 143 patients in the followup study.
[16] Excluding lung cancer, chronic bronchitis, ischemic heart disease, and stroke.
[17] Ongoing study modified for passive smoking.
[18] No overall percentages given.
[19] Two control groups: 15 to 65 and 35 to 85 for both cases and controls in groups 1 and 2, respectively.
[20] Two control groups were randomly chosen from the cohort under study.
[21] Patients in the same or adjacent wards with other diseases.
[22] Entire study population, including smokers.
[23] Frequency matched by 5-year age group to age distribution of cases reported in study area 2 years prior to initiation of study.

*Data not available.

studies from Japan, KATA, does not appear in most of the tables because the odds ratio cannot be calculated.) The studies differ by size, however, which has to be taken into account in analysis. There are two large cohort studies, GARF(Coh) and HIRA(Coh), conducted in the United States and Japan, respectively, and two very small ones, BUTL(Coh) and HOLE(Coh), from the United States and Scotland, respectively. There are two exceptionally large case-control studies--FONT and WUWI of the United States and China; the first was designed specifically to assess the association between ETS and lung cancer, whereas the second has broader exploratory objectives.

The accrual periods of the case-control studies are typically 2 to 4 years in length (exceptions with longer periods are AKIB [9 years], INOU [10 years], GARF [10 years], KABA [19 years], and PERS [9 years]) and occur between the early 1970s and late 1980s (exceptions are KABA [1961-1980] and PERS [1961-1980]). The two large cohort studies were conducted relatively early (GARF(Coh), 1959-72; HIRA(Coh), 1965-81). Differences in study duration or accrual period should not be consequential for hazard identification, which is the topic addressed in this chapter, but both factors affect the estimation of population risk (Chapter 6). Earlier study results are more uncertain for projection of current risk, and parameter values used for modeling are more uncertain when based on extended study periods. Table 5-2 also demonstrates variability across studies in the percentages of cases and controls classified as exposed to ETS. For example, at the extremes for U.S. studies alone, BUFF and BROW classify 84% and 15% of controls as exposed to ETS, respectively. Statistical variability and differences across subpopulations sampled are partially explanatory, but a major factor is differences between researchers' criteria for classification of subjects as exposed to ETS. This issue affects study comparability and observed values of relative risks, which affect both hazard identification and characterization of population risk.

Another example of a study feature of broad consequences in both case-control and cohort studies is the method of diagnosis or confirmation of lung cancer and exclusion of secondary lung cancers in subjects classified as having lung cancer, as shown in Table 5-4. Accurate classification of subjects vis-a-vis the presence or absence of primary lung cancer is essential to the validity of results; inaccurate classification can reduce the chance of detecting a positive association between ETS exposure and lung cancer, if it exists, by biasing the observed relative risk toward unity. (*Note*: "Relative risk" is used to mean the estimate of the true [but unknown] relative risk. For case-control studies, the estimate used is the odds ratio. For editorial convenience, "relative risk" is used for both case-control and cohort studies.)

The large majority of the studies (27 of 31 total) are of the case-control type, which are subject to more potential sources of bias than the cohort studies (see discussion in Section 5.4.1).

Table 5-4. Diagnosis, confirmation, and exclusion of lung cancer cases

	Diagnosis/Confirmation (%)[1]					
Study	Histology		Cytology	Radio./clinical	Other/unspec.	Excluded secondary LC[2]
AKIB[3]	53		4	43	0	Y
BROW	———	100	———			Y
BUFF[3,4]	———	100	———			Y
CHAN[3,4]	82				18	N
CORR[3]	97				3	Y
FONT	100					Y
GAO[3,5]	43		38	19	10	Y
GARF[5]	100					Y
GENG[3]	85			4	11	N
HUMB[6,7]	———	83	———		17	Y
INOU	*		*	*	*	N
JANE[3]	99			1		Y
KABA	100					Y
KALA	48		38		14	Y
KATA	100					N
KOO	94				6	Y
LAMT	———	100	———			Y
LAMW	———	100	———			Y
LEE	*		*	*	*	N
LIU[8]	———	17	———	83	0	N
PERS	83		16		1	Y
SHIM	100					Y
SOBU	100					Y
SVEN[3]	70		29		1	Y
TRIC[3]	28		37	35		N
WU	100					Y
WUWI[3]	42		32	26		Y
BUTL(Coh)[9]		100				Y
GARF(Coh)	*		*	*		N

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Table 5-4. (continued)

Study	Diagnosis/Confirmation (%)[1]			Other/ unspec.	Excluded secondary LC[2]
	Histology	Cytology	Radio./ clinical		
HIRA(Coh)	*	*	*		N
HOLE(Coh)[10]	*	*	*		N

[1] Figures apply to confirmation of original diagnosis when conducted.
[2] Y (for "yes") if specifically indicated; otherwise, N (for "no").
[3] Not restricted to never-smokers (contains former smokers or ever-smokers).
[4] Inconsistency in article. May be 100% histology.
[5] Diagnostic information was reviewed for study.
[6] Includes males.
[7] Available histologic specimens (17 cases) reviewed by pathologists. Poor agreement between review diagnoses and original cancer registry diagnoses (8 of 17 cases). Only reviewed cases, however, are presented in article.
[8] Includes male ever- and never-smokers and one female ever-smoker (control).
[9] Includes one former smoker.
[10] Death certificate diagnosis checked against Scottish cancer registry records.

*Data not available.

To continue the overview depicting some basic similarities and differences between studies that may affect analysis of their results, some additional characteristics of the case-control studies alone are summarized in Table 5-3. The percentage of proxy response is high for some studies, but there is little basis for assessing the direction or magnitude of potential bias from this source. The age range of subjects differs across studies, but there is insufficient information on age distributions within studies to evaluate the effect of age or to adjust for differences between studies. The source of control subjects is a potential source of bias in some studies.

The table heading "ETS sample matched" refers to whether design matching applies to the ETS subjects (the never-smokers used for ETS/lung cancer analysis). As indicated under "matched variables," controls are virtually always matched (or at least similar) to cases on age and usually on several other variables as well that the researcher suspects may affect comparability of cases and controls. The matching often refers to a larger data set than the ETS subjects only, however, because many studies included smokers and investigated a number of issues in addition to whether passive smoking is associated with lung cancer. When the data on ETS subjects are extracted from the larger data set, matching is not retained unless smoking status was one of the matching variables.

Although matching is commonly used as a method to reduce potential confounding, effective techniques also may be implemented during analysis of the data (e.g., the use of poststratification or logistic regression adjustment for unmatched, stratified, or frequency-matched samples). Use of a method of analysis that adjusts for known or suspected confounders and factors that may interact with ETS exposure to affect risk of lung cancer is particularly important for studies that are not designated as "ETS sample matched" in Table 5-3. Even with matched data, a method of analysis that controls for confounding, such as the use of matched pairs or regression techniques, is preferable. In fact, Breslow and Day (1980, p. 32) describe the main purpose of matching in a case-control study as permitting use of efficient analytical methods to control confounding by the factors used for matching.

The analysis for hazard identification in this report follows two approaches. The first approach (Section 5.3) treats all studies equally, i.e., statistical methods are applied to all studies without regard to differences in study utility for the task of hazard identification. Differences in study size, of course, are taken into account by the statistical methods. Statistical inference includes estimation, with confidence intervals, and hypothesis testing for an effect (an increased relative risk in ETS-exposed subjects) and for an upward trend (an increase in relative risk as some measure of ETS exposure increases). The second approach (Section 5.5) is motivated by the heterogeneity of the study evidence, as described above. Study size aside, some studies have higher utility than others for assessing questions related to ETS and lung cancer and thus should be given more weight. To implement this extended data interpretation, all studies are first reviewed individually for sources of bias and confounding that might affect interpretation of results for assessing ETS and lung cancer and then assigned a tier number from 1 to 4 accordingly. Tier 1 contains those studies of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. (*Note:* Study utility does not mean study quality. Utility is evaluated with respect to the research objectives *of this report*, while the objectives of individual studies often differ.) Pooled estimates of relative risk by country are then recalculated by tiers, beginning with the studies of highest utility (Tier 1) and adding studies from Tiers 2, 3, and 4 successively to see what effect a judgment of utility has on the overall outcome in each country. The criteria used in evaluating studies and the procedure for assigning them to tiers are described in Appendix A, which also contains the individual study reviews.

The selection of the most appropriate relative risk estimate to be used from each study is addressed in Section 5.2.1. In Section 5.2.2, each chosen relative risk estimate is adjusted downward to account for bias expected from some smokers misrepresenting themselves as nonsmokers. This topic has been a contentious issue in the literature for several years, with claims that this one source of systematic upward bias may account entirely for the excess risk observed in epidemiologic studies. Recent detailed investigation of this topic by Wells and Stewart (unpublished) make that claim unlikely (Appendix B). They found that a reasonable correction for bias, calculated on a study-by-study basis, is positive but small. Following this methodology, this report makes reductions in the relative risk estimates at the outset for each study individually before statistical inference or pooling estimates from studies of the same country. This is in contrast to the NRC report (1986), which makes the same downward adjustment to all studies (applied to an overall estimate of relative risk obtained after pooling all study estimates).

The estimates adjusted for smoker misclassification bias are the basis for statistical inference in Sections 5.3 (without regard to tier classification) and 5.5 (analysis by tier classification). Section 5.4 reviews the study results on potential modifying factors. Conclusions are then drawn for hazard identification (i.e., whether ETS is causally associated with increased lung cancer mortality) based on the total weight of evidence. Chapter 6 of this report addresses the upward adjustment on the U.S. relative risk estimate for background ETS exposures and the U.S. population risk of lung cancer from ETS.

5.2. RELATIVE RISKS USED IN STATISTICAL INFERENCE

5.2.1. Selection of Relative Risks

Two considerations largely affect the choice of relative risk (RR): (1) whether other relevant cofactors are taken into account (namely, potential confounders and risk modifiers that may be correlated with ETS exposure), and (2) the source and place of ETS exposure used. The alternatives (not yet adjusted for smoker misclassification) are shown by study in Tables 5-5 and 5-6, with the ones selected for analysis in this report in boldface type. Table 5-5 lists the RRs and their confidence intervals, along with explanatory footnotes, and Table 5-6 provides information on source and place of exposure and on the adjusted analysis. Because most studies include spousal smoking, and interstudy comparisons may be useful, spousal smoking was the preferred ETS surrogate in all except for LAMW and SOBU. In LAMW, spousal smoking data are limited to cases with adenocarcinoma; in SOBU, the data for cohabitants are separate from data for spousal smoking, and much of the ETS exposure appears to result from the cohabitants. Only data for broader exposure to ETS than spousal smoking alone were collected in BUFF, CHAN, SVEN, and HOLE(Coh).

Table 5-5. Estimated relative risk of lung cancer from spousal ETS by epidemiologic study (crude and adjusted for cofactors)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
AKIB	1.52 (0.96, 2.41)	1.5 (1.0, 2.5)
BROW	1.52[4] (0.49, 4.79)	*
	1.82[4,5] (0.45, 7.36)[6]	1.68[4,5] (0.39, 6.90)[6]
BUFF	0.81[7] (0.39, 1.66)	*
CHAN	0.75[5] (0.48, 1.19)	*
CORR	2.07[8] (0.94, 4.52)	*
FONT[9]	1.37 (1.10, 1.69)	1.29 (1.03, 1.62)
	1.21 (0.94, 1.56)	1.28 (0.98, 1.66)
	1.32 (1.08, 1.61)	*
GAO	1.19 (0.87, 1.63)	1.34[10,11]
GARF	1.31 (0.93, 1.85)	1.70[12] (0.98, 2.94)[6]
GENG	2.16 (1.21, 3.84)	*
HIRA[13]	1.53[10] (1.10, 2.13)	1.64[10] *
HUMB	2.34 (0.96, 5.69)	2.2 (0.9, 5.5)
INOU	2.55[14] (0.90, 7.20)	2.54[10,15] *
JANE	0.86 (0.57, 1.29)	0.93/0.44[16]

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Table 5-5. (continued)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
KABA[17]	0.79 (0.30, 2.04)	*
KALA	1.62[18] (0.99, 2.65)	1.92 (1.02, 3.59)[6]
	1.41 (0.78, 2.55)	*
KATA	*[19]	*
KOO	1.55 (0.98, 2.44)	1.64
LAMT	1.65 (1.22, 2.22)	*
LAMW	2.51[20] (1.49, 4.23)	*
LEE	1.03 (0.48, 2.20)	0.75/1.60[21]
LIU	0.74 (0.37, 1.48)	0.77 (0.35, 1.68)
PERS	1.28 (0.82, 1.98)	1.2 (0.7, 2.1)[6]
SHIM	1.08[22] (0.70, 1.68)	*
SOBU	1.06[18] (0.79, 1.44)	1.13[18] (0.78, 1.63)[6]
	1.77 (1.29, 2.43)	1.57 (1.07, 2.31)[6]
SVEN	1.26[5] (0.65, 2.48)	1.4[5]
TRIC	2.08[23] (1.31, 3.29)	*
WU	1.41[24] (0.63, 3.15)	1.2 (0.6, 2.5)[6]
WUWI	0.79 (0.64, 0.98)	0.7

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Table 5-5. (continued)

	Never-smokers	
Case-control	Crude RR[1,2]	Adj. RR[1,2,3]
BUTL(Coh)	2.45[25]	**2.02** **(0.48, 8.56)**[6]
GARF(Coh)	*	**1.17**[10] **(0.85, 1.61)**[6]
HIRA(Coh)	**1.38** **(1.03, 1.87)**	1.61 *
HOLE(Coh)[26]	2.27 (0.40, 12.7)	**1.99** **(0.24, 16.7)**[6]

[1] Parentheses contain 90% confidence limits, unless noted otherwise. When not represented in the original studies, the crude ORs and their confidence limits were calculated (or verified) by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. Odds ratios are shown for case-control studies; relative risks are shown for cohort studies.

[2] ORs for never-smokers apply to exposure from spousal smoking, unless indicated otherwise.

[3] Calculated by a statistical method that adjusts for other factors (see Table 5-3), but not corrected for smoker misclassification.

[4] Adenocarcinoma only. Data for crude OR values communicated from author (Brownson).

[5] Exposure at home and/or at work.

[6] 95% confidence interval.

[7] Exposure to regularly smoking household member(s). Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.

[8] Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.

[9] The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15-0.18.

[10] Composite measure formed from categorical data at different exposure levels.

[11] For GAO, data are given as (number of years lived with a smoker, adjusted odds ratio [OR]): (<20, 1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).

[12] Estimate for husband smoking 20 cig./day.

[13] Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study. This case-control study is not counted in any summary results where HIRA(Coh) is included.

[14] OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.

[15] For INOU, data are given as (number of cig./day smoked by husband, adj. OR): (<19, 1.58), (20+, 3.09).

[16] From subject responses/from proxy responses.

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Table 5-5. (continued)

[17] For second KABA study (see addendum in study description of KABA in Appendix A), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.

[18] For the first value, "ETS-exposed" means the spouse smokes; for the second value, "ETS-exposed" means a member of the household other than the spouse smokes.

[19] OR is not defined because number of unexposed subjects is zero for cases or controls.

[20] Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).

[21] From subject responses/from spouse responses.

[22] From crude data, estimated to be: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.

[23] Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).

[24] Raw data for WU are from Table 11 of Surgeon General's report (U.S. DHHS, 1986). Data apply to adenocarcinoma only.

[25] RR is based on person-years of exposure to spousal smoking. "Prevalence" in those units is 20%.

[26] RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adjusted RR is 1.39 (95% C.I. = 0.29, 6.61).

*Data not available.

Table 5-6. Effect of statistical adjustments for cofactors on risk estimates for passive smoking[1]

Case-control study	Exposure		Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
	Source[2]	Place[3]				
AKIB	Sp	A	1.52	1.5	A,L,O,V	LR
BROW	Sp	A	1.52	*	*	*
	A	P	1.82	1.68	A,I,O	LR
BUFF	Co	H	0.81	*	*	*
CHAN	A	A	0.75	*	*	*
CORR	Sp	A	2.07[7]	*	*	*
	M(C)	A	1.66[7]	1.36[7]	Sm	R
FONT	Sp	A	1.37[8]	1.29[8]	A,E,I,L,R	LR
	Sp	A	1.21[9]	1.28[9]	A,E,I,L,R	LR
GAO	Sp	A	1.19	1.34[10]	A,E	R
	A	A	*	0.9	A	LR
GARF	Sp	H	1.31	1.70	A,SES,H,Yd	R
GENG	Sp	A	2.16	*	*	*
HIRA	Sp	A	1.53[10]	1.64[10]	A,F,Oh,	S
	Sp	A	1.53	1.50	F	S
HUMB	Sp	A	2.34	2.2	A,R	R
INOU	Sp	A	2.55	2.54[10]	A	S
JANE	Sp	A	0.86	0.93/0.44[11]	A,L,R	M,S
	A(C)	H	*	1.09/2.07[12]	A,R	
KABA	Sp	A	0.79	*	*	*
KALA	Sp	A	1.62	1.92	A,E,Ir	LR
	OC	H	1.41	*	*	*
KOO	Sp	A	1.55	1.64	A,E,B,Yc	LR
	Co	H	1.34	1.68	A,E,B,Yc	LR
LAMT	Sp	A	1.65	*	*	*

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Table 5-6. (continued)

Case-control study	Exposure		Crude RR[4]	Adj. RR[4]	Adjustment factor(s)[5]	Adj. technique[6]
	Source[2]	Place[3]				
LAMW	Sp	*	2.01[13]	*	*	*
	A	*	**2.51**[14]	*	*	*
LEE	Sp	A	1.3[15]	1.60[15]	A	S
			0.75	0.75		
			[1.03	1.00]		
	Co	H	0.80	0.87[10]	A	S
LIU	Co	A	0.74	**0.77**	C	LR
PERS	Sp	A	1.28	1.2	A,V	M
	Sp	A	1.28	1.47[10]	A	S
SHIM	Sp	H	**1.08**	*	*	*
SOBU	Sp	A	1.06	1.13	A,E	S
	OC	A	1.77	**1.57**	A,E	S
SVEN	A	H,W	1.1/1.8[16]	1.2/2.1[16]	A	S
			(1.26)	(1.4)		
TRIC	Sp	A	**2.08**	*	*	*
WU	Sp	A	**1.41**[17]	1.2	A,L	M
					As	LR
WUWI	Sp	P	**0.79**	0.7	A,E,L	LR
	Co	P	0.78	0.7	A,E,L	LR
BUTL (Coh)	Sp	A	2.45	**2.02**	A	S
GARF (Coh)	Sp	A	*	1.27/1.10[18]	A	S
				1.17	A,E,L,R,Oh	S
				1.37/1.04[18]		
HIRA (Coh)	Sp	A	**1.38**	1.61	Ah	S
HOLE (Coh)	Co	A	2.27	**1.99**	A,SES	S

[1] Values used for inference in this report are shown in boldface.
[2] Source: A = anyone; (C) = childhood; Co = cohabitant(s); M = mother; OC = cohabitant(s) other than spouse; Sp = spouse.
[3] Place: A = anywhere; H = home/household; P = proximity of subjects; W = workplace.
[4] OR for case-control studies; RR for cohort studies.

(continued on the following page)

Table 5-6. (continued)

[5] Adjustment factors: A = age of subject; Ah = age of husband; As = age started smoking; B = number of live births; C = cooking habits; E = education; F = fish consumption; H = hospital; I = income; Ir = interviewer; L = location; O = occupation of subject; Oh = occupation of husband; R = racial or ethnic group; SES = socioeconomic status; Sm = active smoking; V = vital status; Yc = years since exposure ceased; Yd = year of diagnosis.

[6] LR = logistic regression; R = regression; M = matched analysis; S = stratified.

[7] Bronchioalveolar carcinoma excluded. Spousal smoking OR = 1.77 with bronchioalveolar carcinoma excluded; no corresponding value reported for maternal smoking.

[8] Population controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.52 and 1.47, respectively).

[9] Colon cancer controls, all cell types (crude and adjusted ORs for adenocarcinoma alone are 1.35 and 1.44, respectively).

[10] Composite measure formed from categorical data at different exposure levels.

[11] Cases and controls matched on A, L, and N; first value is from subject; second value is from proxy sources.

[12] 1-24 smoker-years/≥ 25 smoker-years.

[13] Adenocarcinoma only.

[14] All cell types.

[15] First value is for smoking information provided by patient's spouse; second value is for information provided by patient herself; third value (in brackets) utilizes available data from either source with subject classified as exposed if either source so indicates.

[16] Exposed at home but not at work or vice versa/exposed both at home and at work followed by weighted average of exposed strata.

[17] Crude OR from Table 11 of Surgeon General's report (U.S. DHHS 1986); note that adjusted OR from WU is not restricted to never-smokers and analysis includes only adenocarcinoma.

[18] Spouse smokes 1-20 cig. per day/spouse smokes ≥ 20 cig. per day. The composite RR is 1.17.

*Data not available.

After exposure source and place are taken into account in the choice of RR values in Table 5-6, an adjusted RR is considered preferable to a crude RR unless the study review in Section A.4 indicates a problem with the adjustment procedure. Of the 31 studies, 20 provide both an adjusted and crude RR, where the "adjusted estimate" is based on the author's use of a statistical procedure that takes potential confounding factors into account, usually by stratification or logistic regression. Based on the decision rule just described, our choice of RR is the smaller of the crude and adjusted values in 14 of the 20 studies providing both estimates. In several studies, RR values in addition to those shown in Table 5-6 might be considered (see Table 5-7). They were not found to be the best choices, however, for comparison between studies.

5.2.2. Downward Adjustment to Relative Risk for Smoker Misclassification Bias

There is ample evidence that some percentage of smokers, which differs for current and former smokers, misrepresent themselves as never-smokers (sometimes the wording of a

Table 5-7. Alternative estimates of lung cancer relative risks associated with active and passive smoking

Study	Active/ passive	ETS exposure	Controls exp. (%)	Alternative estimate	Comparison estimate[1]
BUFF[2]	Passive	Household members regularly smoking for 33+ years	71	Crude OR 0.95 (0.38, 2.40)	0.81
FONT[3]	Passive	Spousal smoking, all types	63	Crude OR 1.52[4] (1.19, 1.96)	1.37
				Adj. OR 1.47	1.29
			66	Crude OR 1.35[5] (1.02, 1.80)	1.21
				Adj. OR 1.44	1.28
			64	Crude OR 1.47[6] (1.15, 1.87)	1.32
				No adj. OR	*
HUMB[7]	Passive	Spousal cigarette smoking[7]	57	Crude OR 1.8 (0.6, 5.4)	2.3
				adj. OR 1.7	2.2
KOO[8]	Passive	Home and/or workplace exposure over lifetime[8]	64	Crude OR 1.36 (0.83, 2.21)	1.34
				Adj. OR 1.86	1.64
PERS[9]	Active	N.A.[10]	37[11]	Crude OR 4.2	*
SHIM[12]	Passive	Total household ETS exposure[12]	77	Crude OR 1.36	1.08
BUTL (Coh)	Active	N.A.[10]	14[11]	Adj. RR 4.0[13]	*
HIRA[14] (Coh)	Active	N.A.[10]	44[11]	Adj. RR 3.79	2.67
HOLE[15] (Coh)	Active	N.A.[10]	56[11]	Adj. RR 4.2	*

[1] Nearest equivalent from Tables 5-5 or 5-6.

[2] Values in Tables 5-5 and 5-6 include household smoking for any duration. Lung cancer may have a long latency period, however, so the extended exposure may be of interest.

[3] As in Table 5-5 except for adenocarcinoma alone.

[4] Population controls only.

[5] Colon cancer controls only.

[6] Control groups combined.

[7] Values in Tables 5-5 and 5-6 include spousal smoking of cigars and pipes.

[8] Value in Table 5-6 is for household cohabitant smoke exposure during adulthood.

(continued on the following page)

Table 5-7. (continued)

[9] Estimate is based on papers by Cederlöf et al. (1975) and Floderus et al. (1988) describing larger populations on which Pershagen study was based.

[10] Not applicable because alternative estimate is for active smoking.

[11] Percentage ever-smokers.

[12] Composite estimate from crude ORs for exposure from husband, parents, and father-in-law. Values in Tables 5-5 and 5-6 consider only spousal smoke exposure.

[13] Rough estimate based on data in Fraser et al. (1991). The prevalence of female ever-smoking is estimated from KALA and TRIC studies, which were conducted in similar conservative societies.

[14] Compares active smokers with never-smokers unexposed to ETS, thus providing a reference group more truly unexposed to tobacco smoke. The value in Table 5-5 is the more conventional comparison of ever-smokers with never-smokers, regardless of passive smoking status.

[15] Estimate is from adjusted RR for both sexes combined with assumption that female RR is 75% of male RR.

*Data not available.

questionnaire may not be explicit enough to distinguish former smokers from never-smokers) (see Appendix B). It has been argued that the resultant misclassification of some smokers as nonsmokers produces an upward bias in the observed relative risk for lung cancer from ETS exposure (i.e., the observed RR is too large). The essence of the supporting argument is based on smoking concordance between husband and wife--a smoker is more likely than a nonsmoker to have been married to a smoker. Consequently, the smoker misclassified as a nonsmoker is more likely to be in the ETS-exposed classification as well. Because smoking causes lung cancer, a misclassified smoker has a greater chance of being a lung cancer case than a nonsmoker. The net effect is that an observed association between ETS exposure and lung cancer among people who claim to be never-smokers may be partially explainable by current or former active smoking by some subjects.

The potential for bias due to misreported smoking habits appears to have been noted first by Lee (see discussion in Lehnert, 1984), and he emphasizes it in several articles (e.g., Lee, 1986, 1987a,b). In Lee, 1987b, it is argued that smoker misclassification may explain the entire excess lung cancer risk observed in self-reported never-smokers in epidemiologic studies. Lee's estimates of bias due to smoker misclassification appear to be overstated, however, for reasons discussed in Appendix B.

The NRC report on ETS (1986) devotes considerable attention to the type of adjustment for smoker misclassification bias. It follows the construct of Wald and coworkers, as described in Wald et al., 1986; Wald was the author of this section in the 1986 NRC report. An illustrative diagram for the implicit true relative risk of lung cancer from exposure to ETS in women from spousal smoking is shown in Figure 2 of Wald et al. (1986). A similar example is in Table 12-5 of the NRC report.

Both Lee's and Wald's work adjust an overall relative risk estimate, pooled over several studies, downward, rather than address each individual study, with its own peculiarities, separately. Furthermore, statistical analysis over the studies as a whole is conducted first, and then an adjustment is made to the overall relative risk estimate. The recent work of Wells and Stewart (Appendix B) on this subject makes an adjustment to each individual study separately. Consequently, the pertinent adjustment factors that vary by study and type of society can be tailored to each study and then applied to the observed data before any statistical analysis. The latter procedure is applied in this report.

The methodology to adjust for bias due to smoker misclassification and the details of its application to the ETS studies are provided in Appendix B. The results of the adjustment and estimate of bias are given in Table 5-8. In general, the biases are low in East Asia, or in any traditional society such as Greece, where female smoking prevalence is low and the female smoker risk is low. Some of the calculated biases are slightly less than unity when carried to three decimal places. This may result from the assumption in the calculations that there is no passive smoking effect on current smokers.

5.3. STATISTICAL INFERENCE

5.3.1. Introduction

Table 5-9 lists the values of several statistical measures for the effect of spousal smoking by study (see boldface entries in Table 5-6 for details). Their meanings will be described before proceeding to interpretation of the data, even though the concepts discussed may be familiar to most readers. The p-values refer to a test for effect and a test for trend. In the former, the null hypothesis of no association (referred to as "no effect" of ETS exposure on lung cancer risk) is tested against the alternative of a positive association. The test for trend applies to a null hypothesis of no association between RR and exposure level against the alternative of a positive association. When data are available on more than two levels of intensity or duration of ETS exposure, typically in terms of the husband's smoking habit (e.g., cig./day or years of smoking), then a test for trend is a useful supplement in testing for an effect, as well as indicating whether a dose-response relationship is likely.

The entries under "power" in Table 5-9 are calculated for the study's ability to detect a true relative risk of 1.5 and a decision rule to reject the null hypothesis of no effect when $p < 0.05$ (see Dupont and Plummer [1990] for methods to calculate power). The power is the estimated probability that the null hypothesis would be rejected if the true relative risk is 1.5 (i.e., that the

Table 5-8. Estimated correction for smoker misclassification

	Never-smokers RR[1]				
Case control	Uncorrected[2] (1)		Corrected[3] (2)	Bias[4] (1)/(2)	Ever-smokers OR used[5]
AKIB	———	1.5 (1.0, 2.5)	———	1.00	2.38
BROW	1.52 (0.49, 4.79)		1.50 (0.48, 4.72)	1.01	4.30
BUFF	0.81 (0.39, 1.66)		0.68 (0.32, 1.41)	1.20	7.06
CHAN	0.75 (0.48, 1.19)		0.74 (0.47, 1.17)	1.01	3.48
CORR	2.07 (0.94, 4.52)		1.89 (0.85, 4.14)	1.10	12.40
FONT	1.29 (1.03, 1.62)		1.28 (1.03, 1.60)	1.01	8.0
GAO	———	1.19 (0.87, 1.63)	———	1.00	2.54
GARF	1.31 (0.93, 1.85)		1.27 (0.91, 1.79)	1.03	6.0
GENG	———	2.16 (1.21, 3.84)	———	1.00 (0.995)	2.77
HIRA	1.53 (1.10, 2.13)		1.52 (1.10, 2.12)	1.01	3.20
HUMB	2.2 (0.9, 5.5)		2.00 (0.83, 4.97)	1.10	16.3
INOU	———	2.55 (0.90, 7.20)	———	1.00 (0.996)	1.66
JANE	0.86 (0.57, 1.29)		0.79 (0.52, 1.17)	1.09	8.0
KABA	0.79 (0.30, 2.04)		0.73 (0.27, 1.89)	1.08	5.90
KALA	———	1.92 (1.13, 3.23)	———	1.00	3.32
KATA	*		*	*	*
KOO	1.55 (0.98, 2.44)		1.54 (0.98, 2.43)	1.01	2.77
LAMT	1.65 (1.21, 2.21)		1.64 (1.21, 2.21)	1.01	3.77

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Table 5-8. (continued)

Case control	Never-smokers RR[1] Uncorrected[2] (1)		Corrected[3] (2)	Bias[4] (1)/(2)	Ever-smokers OR used[5]
LAMW	____	2.51 (1.49, 4.23)	____	1.00 (0.996)	4.12
LEE	1.03 (0.48, 2.20)		1.01 (0.47, 2.15)	1.02	4.61
LIU	____	0.77 (0.35, 1.68)	____	1.00	*
PERS	1.2 (0.7, 2.1)[6]		1.17 (0.75, 1.87)	1.03	4.2
SHIM	1.08 (0.70, 1.68)		1.07 (0.7, 1.67)	1.01	2.8
SOBU	____	1.57 (1.13, 2.15)	____	1.00	2.81
SVEN	1.26 (0.65, 2.48)		1.20 (0.63, 2.36)	1.05	6.00
TRIC	____	2.08 (1.31, 3.29)	____	1.00	2.81
WU	1.41 (0.63, 3.15)		1.32 (0.59, 2.93)	1.07	4.38
WUWI	0.79 (0.64, 0.98)		0.78 (0.63, 0.96)	1.01	2.24
BUTL (Coh)	2.02[7] (0.48, 8.56)[6]		2.01 (0.61, 6.73)	1.00	4.0
GARF (Coh)	1.17[7] (0.85, 1.61)[6]		1.16 (0.89, 1.52)	1.01	3.58
HIRA (Coh)	1.38 (1.03, 1.87)		1.37 (1.02, 1.86)	1.01	3.20
HOLE (Coh)	1.99[7] (0.24, 16.7)[6]		1.97 (0.34, 11.67)	1.01	4.2

[1] OR for case-control studies; RR for cohort studies.

[2] Adjusted OR in Table 5-5 is used unless the confidence interval is unknown or the study review (Appendix A) is critical of the method(s) used.

[3] Corrected (2) (estimate and confidence interval) equals uncorrected (1) times ratio [(2)/(1)]. All corrected 95% confidence intervals have been converted to 90% confidence intervals.

[4] Values shown are the lower of (calculated ratio, 1). Calculated ratios less than 1 are shown in parentheses.

[5] The crude OR for ever-smokers in Table 5-5 is used in the calculations for the corrected value (Appendix B), when available. Ever-smoker ORs for GARF, JANE, PERS, and SHIM are approximated from the data of other studies for suitable location and time period. The ever-smoker ORs for BUTL(Coh) and (LEE) are based on data in Fraser et al. (1991) and Alderson et al. (1985), respectively.

[6] 95% confidence interval.

[7] Adjusted RR value in Table 5-5.

Table 5-9. Statistical measures by individual study and pooled by country, corrected for smoker misclassification[1]

Location	Study	Relative weight[2] (%)	Power[3]	P-value		RR[6]	Confidence interval 90%
				Effect[4]	Trend[5]		
Greece	KALA	43	0.39	0.02	0.04	1.92	(1.13, 3.23)
Greece	TRIC	57	0.45	<0.01	<0.01	2.08	(1.31, 3.29)
Greece	**ALL**	**5**		**<0.01**		**2.01**	**(1.42, 2.84)**
HK	CHAN	20	0.43	>0.5	*	0.74	(0.47, 1.17)
HK	KOO	20	0.43	0.06	0.16	1.54	(0.98, 2.43)
HK	LAMT	45	0.73	<0.01	<0.01	1.64	(1.21, 2.21)
HK	LAMW	15	0.39	<0.01	*	2.51	(1.49, 4.23)
HK	**ALL**	**14**		**<0.01**		**1.48**	**(1.21, 1.81)**
Japan	AKIB	15	0.42	0.05	0.03	1.50	(1.00, 2.50)
Japan	HIRA (Coh)	35	0.75	0.04	<0.01	1.37	(1.02, 1.86)
Japan	INOU	3	0.17	0.07	<0.03	2.55	(0.90, 7.20)
Japan	SHIM	16	0.37[7]	0.38	*	1.07	(0.70, 1.67)
Japan	SOBU	30	0.66	0.01	*	1.57	(1.13, 2.15)
Japan	**ALL**	**19**		**<0.01**		**1.41**	**(1.18, 1.69)**
USA	BROW	1	0.15	0.28	*	1.50	(0.48, 4.72)
USA	BUFF	3	0.17	>0.5	*	0.68	(0.32, 1.41)
USA	BUTL (Coh)	1	0.18	0.17	*	2.01	(0.61, 6.73)
USA	CORR	3	0.22	0.10	0.01	1.89	(0.85, 4.14)
USA	FONT[8]	35	0.93	0.03	0.04	1.28	(1.03, 1.60)
USA	GARF	15	0.60[7]	0.12	<0.02	1.27	(0.91, 1.79)

(continued on the following page)

Table 5-9. (continued)

Location	Study	Relative weight[2] (%)	Power[3]	P-value		RR[6]	Confidence interval 90%
				Effect[4]	Trend[5]		
USA	GARF (Coh)	25	0.92	0.18	*	1.16	(0.89, 1.52)
USA	HUMB	2	0.20	0.10	*	2.00	(0.83, 4.97)
USA	JANE	10	0.44[7]	>0.5	*	0.79	(0.52, 1.17)
USA	KABA	2	0.17[7]	>0.5	*	0.73	(0.27, 1.89)
USA	WU	3	0.21	0.29	*	1.32	(0.59, 2.93)
USA	**ALL**	**34**		**0.02**		**1.19**	**(1.04, 1.35)**
Scotland	HOLE (Coh)	100	0.09	0.26	*	1.97	(0.34, 11.67)
Eng./Wales	LEE	100	0.20	0.50	*	1.01	(0.47, 2.15)
Sweden	PERS	68	0.45[7]	0.27	0.12	1.17	(0.75, 1.87)
Sweden	SVEN	32	0.24	0.31	*	1.20	(0.63, 2.36)
W. Europe	**ALL**	**5**		**0.22**		**1.17**	**(0.84, 1.62)**
China	GAO	28	0.66	0.18	0.29	1.19	(0.87, 1.62)
China	GENG	8	0.32	0.01	<0.05	2.16	(1.21, 3.84)
China	LIU	4	0.18	>0.5	*	0.77	(0.35, 1.68)
China	WUWI	60	0.89[7]	>0.5	*	0.78	(0.63, 0.96)
China	**ALL**	**22**		**>0.5**		**0.95**	**(0.81, 1.12)**

[1] Misclassification is discussed in Section 5.2.2 and Appendix B.
[2] A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3] *A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4] One-sided p-value for test of RR = 1 versus RR > 1.
[5] P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative, i.e., upward trend.
[6] Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[7] Calculated for matched study design.
[8] For population control group only, all cases.

*Data not available; ns = not significant.

correct decision would result; the power would be larger if the true relative risk exceeds 1.5). If the estimates of power for the U.S. studies in Table 5-9 are used for illustration, it can be seen that the estimated probability that a study would *fail* to detect a true relative risk of 1.5 (equal to 1 − Power, the probability of a Type II error [discussed in the next paragraph] when the true relative risk is 1.5) is as follows: FONT, 0.07; GARF(Coh), 0.08; GARF, 0.40; JANE, 0.56; BUFF, 0.83; CORR, 0.78; WU, 0.79; HUMB, 0.80; KABA, 0.83; BUTL(Coh), 0.82; and BROW, 0.85. Thus, 7 of the 11 U.S. studies have only about a 20% chance of detecting a true relative risk as low as 1.5 when taken alone. Sources of bias effectively alter the power in the same direction as the bias (e.g., a downward bias in RR decreases the power). Of the potential sources of bias discussed by study in Section A.4, the predominant direction of influence on the observed RR, when identifiable, appears to be in the direction of unity, thus affecting power adversely. The RRs already have been reduced to adjust for smoker misclassification, the only systematic source of upward bias that has been established.

Studies of all sizes, large and small, are equally likely to make a false conclusion if ETS is not associated with lung cancer risk (Type I error). However, smaller studies are less likely to detect a real association when there is one (Type II error). This imbalance comes from using the significance level of the test statistic to determine whether to reject the null hypothesis. If the decision rule is to reject the hypothesis when the p-value is smaller than some prescribed value (e.g., 0.05), then the Type I error rate is 0.05, but the Type II error rate increases as study size decreases. When a study with low power fails to reject the null hypothesis of no effect, it is not very informative because that outcome may be nearly as likely when the null hypothesis is false as when it is true. When detection of a small relative risk is consequential, pooling informational content of suitably chosen studies empowers the application of statistical methods.

The heading in Table 5-9 that remains to be addressed is "relative weight," to be referred to simply as "weight." When the estimates of relative risk from selected studies are combined, as for studies within the same country as shown in the table, the logarithms of the RRs are weighted inversely proportional to their variances (see Appendix D and footnote 2 of Table 5-9). These relative weights are expressed as percentages summing to 100 for each country in Table 5-9. Study weight and power are positively associated, which is explained by the significant role of study size to both. Consequently, studies weighted most heavily (because the standard errors of the RRs are low) also tend to be the ones with the highest power (most likely to detect an effect when present).

5.3.2. Analysis of Data by Study and Country

5.3.2.1. *Tests for Association*

The p-values of the test statistics for the hypothesis of no effect (i.e., RR = 1) are shown in Table 5-9. Values of the test statistics (the standardized log odds ratio; see Appendix D) are plotted in Figure 5-1. Also shown in Figure 5-1 for reference are the points on the horizontal axis corresponding to p-values of 0.5, 0.2, 0.1, 0.05, 0.01, and 0.001. For example, the area under the curve to the right of the vertical line labeled $p = 0.01$ is 0.01 (1%), so it is apparent from Figure 5-1 that three studies had significance levels $p < 0.01$ (more specifically, $0.001 < p < 0.01$). The size of the symbol (inverted triangle) used for a study is proportional in area to the relative weight of that individual study, but of current interest is the location and not the size of the symbol. If the null hypothesis is true, then the plotted values would arise from a standard normal distribution, shown in the figure (points to the left of zero indicate that the RR is less than 1, and points to the right of zero indicate that RR is greater than 1). If the points lie more toward the right side of the normal curve than would be likely to occur by chance alone, then the hypothesis of no effect is rejected in favor of a positive association between ETS exposure and lung cancer. If one constructs five intervals of equal probability (i.e., intervals of equal area under the standard normal curve), the expected number of observations in each interval is six (these five intervals are not shown on Figure 5-1). The observed numbers in these intervals, however, from left to right are 3, 3, 1, 7, and 16, an outcome that is significant at $p < 0.005$, by the chi-square goodness-of-fit test. At the points on the standard normal curve corresponding to p-values 0.5, 0.4, 0.3, 0.2, 0.1, and 0.05, the probability that a number of outcomes as large as that actually observed would occur by chance is less than 0.005 at all points. Consequently, the hypothesis of no effect is rejected on statistical grounds, and that conclusion is not attributable to a few extreme outcomes that might be aberrant in some way.

Figure 5-2 displays the U.S. studies alone (see Appendix D for calculation of the test statistics). Figure 5-3 corresponds to Figure 5-1 except that the test statistics for the hypothesis of no effect (i.e., RR = 1) for the significance levels shown apply to a single overall estimate of RR for each country, formed by statistically pooling the outcomes from the studies within each country. The areas of the symbols for countries are also in proportion to statistical weight as given in Table 5-9. It is implicitly assumed that studies within a country, and the subpopulations sampled, are sufficiently homogeneous to warrant combining their statistical results into a single estimate for the country (see Greenland [1987] for a discussion of applications of meta-analysis to epidemiology). The calculational method employed weights the observed RR from each study within a country inversely proportional to its estimated variance (see Appendix D). The relative

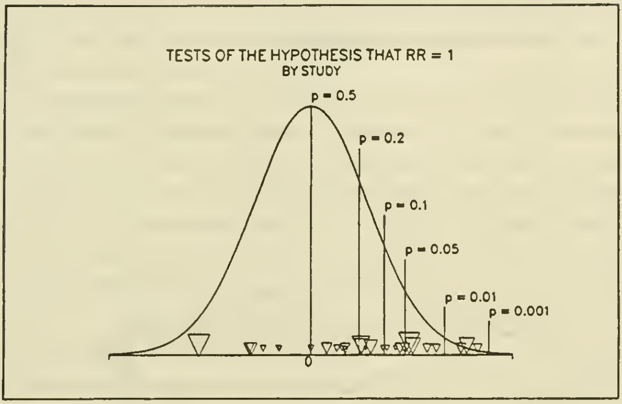

Figure 5-1. Test statistics for hypothesis RR = 1, all studies.

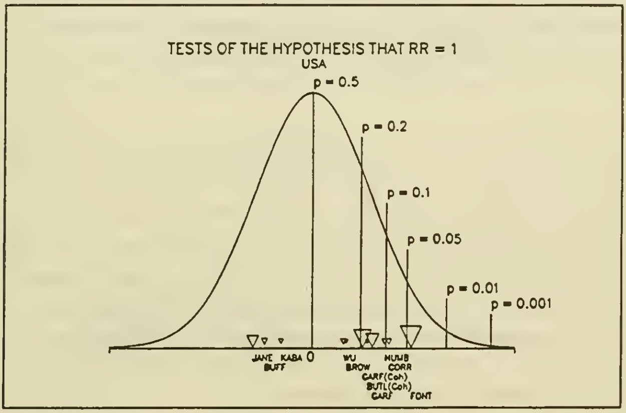

Figure 5-2. Test statistics for hypothesis RR = 1, USA only.

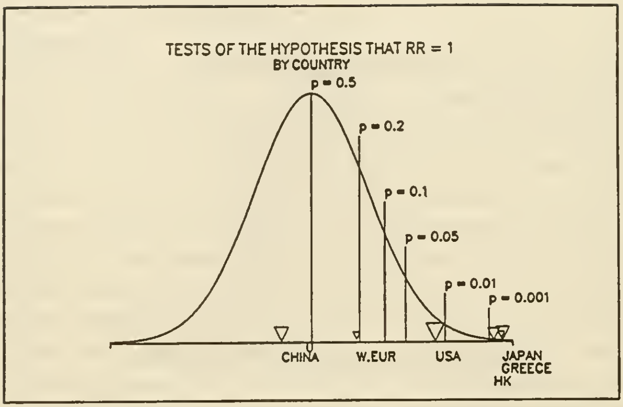

Figure 5-3. Test statistics for hypothesis RR = 1, by country.

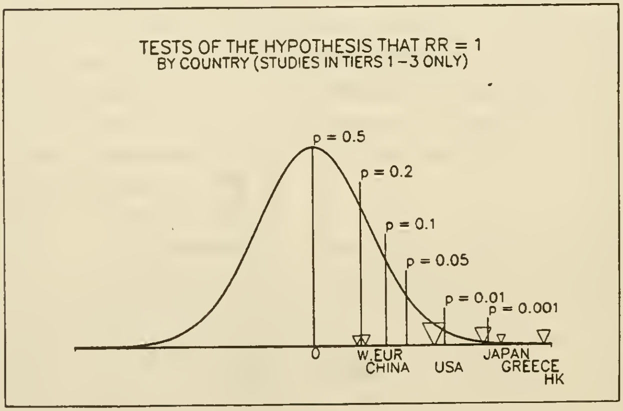

Figure 5-4. Test statistics for hypothesis RR = 1, tiers 1-3 only.

study weights are shown in Table 5-9. Each symbol in Figures 5-1, 5-2, 5-3, and 5-4 has been scaled so that its area is proportional to the weight of the outcome represented, relative to all other outcomes shown in the same figure.

Greece, Hong Kong, and Japan, which together comprise a total weight of 39%, are *each* statistically significant at $p < 0.01$ against the null hypothesis of no increase in relative risk (RR = 1). When the United States is included, the total weight is 73%, and *each* of the four countries is significant at $p < 0.02$. The four studies combined into the group called Western Europe are not large. Together they represent 5% of the total weight, and their combined odds ratio (1.17) is slightly above 1 but not statistically significant ($p = 0.21$). In contrast, China is weighted quite high (22%), the p-value is large (0.66), and the odds ratio is less than 1 (0.95), strongly indicating no evidence of an increase in RR due to ETS. This is largely because China is very heavily influenced by WUWI (relative weight of 60% of China), which is a very large case-control study. However, this apparent inconsistency in WUWI may be due to the presence of indoor smoke from cooking and heating, which may mask any effect from passive smoking. A similar but more extreme situation is found in LIU, conducted in a locale where indoor heating with smoky coal (an established risk factor for lung cancer) and inadequate venting are common. Both WUWI and LIU were conducted primarily to assess the hazardous potential of these pollutants. The indoor environments of the populations sampled in WUWI and LIU make detection of any carcinogenic hazard from ETS unlikely, and thus render these studies to be of little value for that purpose (see discussions of WUWI and LIU in Section A.4). Without WUWI or LIU, the combined results of the two remaining studies in China, GAO and GENG, are significant at $p = 0.03$.

Such qualitative considerations about the likely utility of a study to detect an ETS effect, if one exists, are taken into account in Section 5.5. In that section, studies are ranked into one of four tiers based on their likely utility. Studies such as WUWI and LIU would be placed into Tier 4, the grouping with the least likelihood of providing useful information on the effects of ETS. Figure 5-4 is similar to Figure 5-3 displaying the distribution of test statistics for the pooled estimates by country, but includes only the studies in Tiers 1, 2, and 3; it is shown here for comparison purposes (see Section 5.5 for a detailed discussion of the analysis based on tiers).

5.3.2.2. *Confidence Intervals*

Confidence intervals for relative risk are displayed by study and by country in Table 5-9 (see Appendix D for method of calculation). The 90% confidence intervals by country are illustrated in Figure 5-5. (*Note*: 90% confidence intervals are used for correspondence to a right-

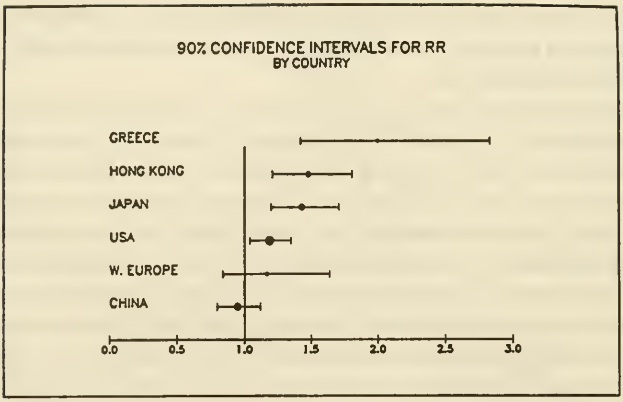

Figure 5-5. 90% confidence intervals, by country.

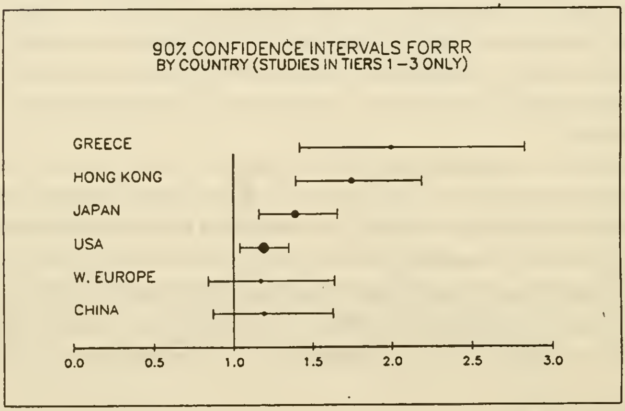

Figure 5-6. 90% confidence intervals, by country, tiers 1-3 only.

tailed test of the hypothesis of no effect at a 5% level of significance.) The area of the symbol (solid circle) locating the point estimate of relative risk within the confidence interval is proportional to study weight. Symbol size is used as a device to draw attention to the shorter confidence intervals, which tend to be based on more data than the longer ones. The confidence intervals for countries jointly labeled as Western Europe are in Table 5-9, except for Sweden which contains two studies, PERS and SVEN. For those two studies combined, the odds ratio (OR) is 1.19 (90% C.I. = 0.81, 1.74). The confidence intervals for the pooled relative risk estimates by country for studies in Tiers 1, 2, and 3 only (see previous paragraph and Section 5.5) are displayed in Figure 5-6.

In descending order, the relative risks in Figure 5-6 are for Greece, Hong Kong, Japan, the United States, and Western Europe. (China is being excluded from this summary because it contains only one study in Tiers 1-3 [GAO], which is unlikely to be representative of such a vast country. The relative risk estimate for that study, 1.19, is similar to the overall relative risks for the United States and Western Europe.) The estimated relative risks from exposure to spousal smoking differ between countries, with Greece, Hong Kong, and Japan at the high end of the scale and the United States and Western Europe at the low end. These differences suggest that combining studies from different countries should be done with caution. The relative risks pertain only to ETS exposure from spousal smoking, which may be a higher proportion of total ETS exposure in some countries than in others. This also emphasizes the importance of taking into account exposure and background (nonspousal) ETS, which is considered in the estimation of population risk for the United States in Chapter 6.

5.3.3. Analysis of Data by Exposure Level

5.3.3.1. *Introduction*

In Section 5.3.2, analyses are conducted by individual study and by studies pooled within countries, using the dichotomous data on spousal smoking (i.e., any level of spousal smoking versus no spousal smoking) as a surrogate for ETS exposure. This section examines the response data from all of the studies that provide data analysis by exposure-level categories. Exposure level, for these studies, refers to the amount of spousal smoking. In different studies, exposure is measured by intensity (e.g., cig./day smoked by the husband), duration (e.g., number of years married to a smoker), or a combination of both (e.g., number of pack-years--packs per day × years of smoking by the husband). The data are analyzed by calculating RR estimates for the highest exposure groups only (Section 5.3.3.2) and then by testing for an upward trend in RR across exposure groups within studies as ETS exposure increases (Section 5.3.3.3).

An evaluation of the highest exposure group or a test for exposure-related trend may be able to detect an association that would be masked in a test for effect using only dichotomous data. This masking is especially likely to occur when dealing with a weak association or a crude surrogate measure for exposure that is widespread (i.e., greater potential for exposure misclassification), both of which are difficulties in studies of ETS and lung cancer.

As discussed in Chapter 3, ETS is a dilute mixture, and, consequently, any association observed between environmental levels of ETS exposure and lung cancer is likely to be weak (i.e., have a low RR). Furthermore, questionnaire-based assessment of exposure to ETS is a crude indicator of actual lifetime exposure, and spousal smoking is an incomplete surrogate for exposure because it does not consider ETS from other sources, such as the workplace. Therefore, exposure misclassification in both directions is inevitable. For example, there will be women whose husbands do not smoke but who are exposed to substantial levels of ETS from other sources, and there will be women whose husbands smoke but who are not actually exposed to appreciable levels of ETS. This latter scenario is most likely if the level of spousal smoking is low. Comparing the highest exposure group with the "unexposed" group will help reduce the effect of this latter type of exposure misclassification bias.

In addition, the detection of an exposure-response relationship (trend) across exposure groups increases support for a causal association by diminishing the likelihood that the results can be explained by confounding, because any potential confounder would have to be associated with both lung cancer and ETS exposure in a dose-related manner. However, the potential for exposure misclassification is compounded when the exposed group is further divided into level-of-exposure categories and the sample sizes become small. This is especially problematic in small studies. These inherent difficulties with the ETS database tend to diminish the possibility of detecting exposure-response relationships. Therefore, the inability to demonstrate an exposure-response trend is not considered evidence against causality; rather, if a statistically significant trend can be detected despite these potential obstacles, it provides evidential support for a causal association.

5.3.3.2. *Analysis of High-Exposure Data*

In this section, analyses will be conducted for the highest exposure groups by study and by studies pooled within countries. As described in Section 5.3.3.1, analyzing only the data from the highest exposure group of each study increases the sensitivity for detecting an association and reduces the effects of exposure misclassification. Fractionating the data, however, does decrease the power to observe statistical significance.

The results of statistical inference using only data from the highest exposure categories are displayed in Table 5-10. As indicated in the table, exposure-level data are available in 17 studies. The definitions of highest exposure category, shown next to the study name in the table, vary widely between studies. Crude RR estimates adjusted for smoker misclassification (see Section 5.2 and Appendix B) are used in this section rather than the estimates adjusted for modifying factors within the studies, because the latter are available by exposure level for only a limited number of studies.

Several observations are apparent from Table 5-10. First, every one of the 17 individual studies shows increased risk at the highest exposure level, even after adjusting for smoker misclassification. Second, 9 of the 16 comparisons for which sufficient data are available are statistically significant ($p \leq 0.05$), despite most having very low statistical power. Third, the RR estimates pooled within countries are each statistically significant with $p \leq 0.02$. Although the RR estimates within a country are pooled across different definitions of highest exposure, which somewhat limits their interpretation and practical value, it is apparent that these RRs are considerably higher than the values observed for the dichotomous data (Table 5-9). The RR estimates pooled by country vary from a low of 1.38 ($p = 0.005$) for the United States to a high of 3.11 ($p = 0.02$) for Western Europe, which contains only one study. Finally, the overall pooled estimate of 1.81 for the highest exposure groups from all 17 studies is highly statistically significant ($p < 0.000001$).

These results are consistent with the statistical evidence presented in Section 5.3.2 for an association between ETS exposure and lung cancer. In fact, increased risks are found for the highest exposure groups without exception. Furthermore, the RR estimates pooled within countries are all statistically significant and range from 1.38 to 3.11, even after adjustment for smoker misclassification. The consistency of these highest exposure results cannot be accounted for by chance, and the stronger associations detected for the highest exposure groups across all countries further reduce the likelihood that bias or confounding could explain the observed relationship between ETS and lung cancer.

In addition, with the exception of Western Europe, which contains only one low-power study in this analysis, the pooled RR estimates from other, more "traditional" countries are all appreciably higher than that from the United States. It is likely that these differences are at least partially a result of higher background (nonspousal) ETS exposures to the allegedly "unexposed" group in the United States. Again, this highlights the importance of accounting for ETS exposures from sources other than spousal smoking. An adjustment for background ETS exposures is made in Chapter 6, for the estimation of population risk for the United States.

Table 5-10. Statistical measures for highest exposure categories only[1]

Location	Study	Highest exposure level	Relative weight[2] (%)	Power[3]	P-value Effect[4]	RR[5,6]	Confidence interval[6] 90%
Greece	KALA	(≥41 cig./day)	35	0.06	0.16	1.57	(0.74, 3.32)
Greece	TRIC	(≥21 cig./day)	65	0.11	0.003	2.55	(1.46, 4.42)
Greece	**All**	**High**	**8**		**0.002**	**2.15**	**(1.38, 3.35)**
Hong Kong	KOO	(≥21 cig./day)	36	0.11	0.36	1.16	(0.58, 2.55)
Hong Kong	LAMT	(≥21 cig./day)	64	0.16	0.02	2.05	(1.18, 3.57)
Hong Kong	**All**	**High**	**8**		**0.03**	**1.68**	**(1.08, 2.62)**
Japan	AKIB	(≥30 cig./day)	6	0.10	0.13	2.1	(0.7, 2.5)
Japan	HIRA (Coh)	(≥20 cig./day)	89	0.13	0.00015	1.91	(1.42, 2.56)
Japan	INOU	(≥20 cig./day)	4	*	0.05	3.09	(1.0, 11.8)
Japan	**All**	**High**	**22**		**<0.00004**	**1.96**	**(1.49, 2.60)**
United States	CORR	(≥41 pack-yrs)	8	0.06	0.005	3.20	(1.53, 6.74)
United States	FONT	(≥80 pack-yrs)	14	*	0.21	1.32[7]	(0.75, 2.29)
United States	GARF	(≥20 cig./day)	15	0.21	0.01	2.05	(1.19, 3.49)
United States	GARF (Coh)	(≥20 cig./day)	45	*	0.33	1.09	(0.81, 1.49)
United States	HUMB	(≥21 cig./day)	2	*	0.46	1.09	(0.27, 4.73)
United States	JANE	(≥50 pack-yrs)	8	*	0.50	1.01	(0.50, 2.04)
United States	WU	(≥31 years)	8[8]	*	*	1.87	*
United States	**All**	**High**	**36**		**0.005**	**1.38**	**(1.13, 1.70)**
W. Europe	PERS	(≥18 cig./day)	100	*	0.02	3.11	(1.18, 7.71)
W. Europe	**All**	**High**	**2**		**0.02**	**3.11**	**(1.18, 7.71)**
China	GAO	(≥40 years)	35	0.33	0.02	1.7	(1.09, 2.65)
China	GENG	(≥20 cig./day)	65	*	<0.00001	2.78	(2.02, 3.84)
China	**All**	**High**	**24**		**<0.000001**	**2.32**	**(1.78, 3.03)**
All	**All**	**High**			**<0.000001**	**1.81**	**(1.60, 2.05)**

(continued on the following page)

Table 5-10. (continued)

[1] Similar to Table 5-9 except entries apply to highest exposure category only in each study. Only studies with data available for categorized measures of exposure are included. Relative risks and confidence bounds are corrected for smoker misclassification.
[2] A study's relative weight (wt) is 1/var (log(OR)), divided by the sum of those terms for all studies included, times 100 (to express as a percentage).
[3] *A priori* probability of significant ($p < 0.05$) test of effect when true relative risk is 1.5.
[4] One-sided p-value for test of RR = 1 versus RR > 1.
[5] Adjusted for smoker misclassification. OR used for case-control studies; RR for cohort studies.
[6] Values may differ from those of Table 5-11, where confidence intervals are shown as they appear in the source. In Table 5-11, the RR and confidence interval are *not* corrected for smoker misclassification, as in this table, and most of the confidence intervals are 95% instead of 90%.
[7] Value shown is for all cell types with the two control groups combined. For adenocarcinoma cases only, the RR is 1.68 with C.I. = 0.81, 3.46.
[8] Relative weight assumed to be the same as for CORR, based on the outcome in Table 5-9.

*Data not available.

5.3.3.3. *Tests for Trend*

In this section, exposure-response data from the studies providing data by exposure level are tested for upward trend. An exposure-response relationship provides strong support for a causal association (see Section 5.3.3.1).

Table 5-11 presents the female exposure-response data and trend test results from the studies of ETS and lung cancer discussed in this report. The p-values reported in the table are for a test of no trend against the one-sided alternative of an upward trend (i.e., increasing RR with increasing exposure). (*Note*: The results for tests of trend are taken from the study reports. Unless the report specified that a one-sided alternative was used, the reported p-value was halved to reflect the outcome for the one-sided alternative of RR increasing with exposure. Where the data are available, the p-values reported by the individual study's authors have been verified here by application of the Mantel, Haenszel test [Mantel, 1963].)

Wu-Williams and Samet (1990) previously reviewed the exposure-response relationships from the epidemiologic studies on ETS then available. They determined that 12 of 15 studies were statistically significant for the trend test for at least one exposure measure. The probability of this proportion of statistically significant results occurring by chance in this number of studies is virtually zero ($p < 10^{-13}$). Intensity of spousal smoking was the most consistent index of ETS exposure for the demonstration of an exposure-response relationship.

Our assessment of the exposure-response data is similar and provides essentially the same results for a slightly different set of studies. Table 5-12 summarizes the p-values of the trend

Table 5-11. Exposure response trends for females

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
AKIB	21	82		1.0		0.03
(cig./day)	29	90	1-19	1.3	(0.7, 2.3)[5]	
	22	54	20-29	1.5	(0.8, 2.8)[5]	
	12	23	≥30	2.1	(0.7, 2.5)[5]	
AKIB	21	82	0	1.0		0.24
(years)	20	30	1-9	2.1	(1.0, 4.3)[5]	
	29	81	20-39	1.5	(0.8, 2.7)[5]	
	22	59	≥40	1.3	(0.7, 2.5)[5]	
CORR	8	72	0	1.00		0.01
(pack-yrs.)	5	38	1-40	1.18	(0.44, 3.20)	
	9	23	≥41	3.52	(1.45, 8.59)	
FONT[6]	*	*	0	1.00		0.07
(years)	*	*	1-15	1.19	(0.88, 1.61)	
	*	*	16-30	1.14	(0.82, 1.59)	
	*	*	>30	1.25	(0.91, 1.72)	
FONT[7]	*	*	0	1.00		0.02
(years)	*	*	1-15	1.33	(0.93, 1.89)	
	*	*	16-30	1.40	(0.96, 2.05)	
	*	*	>30	1.43	(0.99, 2.09)	
FONT[6]	*	*		1.00		0.04
(pack-yrs.)	*	*	0<15	0.96	(0.72, 1.29)	
	*	*	15-39	1.13	(0.81, 1.59)	
	*	*	40-79	1.25	(0.86, 1.81)	
	*	*	≥80	1.33	(0.68, 2.58)	
FONT[7]	*	*		1.00		0.01
(pack-yrs.)	*	*	0<15	1.03	(0.73, 1.46)	
	*	*	15-39	1.26	(0.85, 1.87)	
	*	*	40-79	1.49	(0.98, 2.27)	
	*	*	≥80	1.70	(0.82, 3.49)	
GAO	99	57	0-19	1.0		0.29
(tot. yrs.)[8]	93	63	20-29	1.1	(0.7, 1.8)	
	107	78	30-39	1.3	(0.8, 2.1)	
	76	48	≥40	1.7	(1.0, 2.9)	
GARF	44	157	0	1.00		<0.02
(cig./day)	29	90	1-9	1.15	(0.8, 1.6)	
	17	56	10-19	1.08	(0.8, 1.5)	
	26	44	≥20	2.11	(1.1, 4.0)	
GENG	*	*	0	1.00		<0.05[9]
(cig./day)	*	*	1-9	1.40	(1.1, 1.8)	
	*	*	10-19	1.97	(1.4, 2.7)	
	*	*	≥20	2.76	(1.9, 4.1)	

(continued on the following page)

Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
GENG	*	*	0	1.00		<0.05[9]
(years)	*	*	<20	1.49	(1.15, 1.94)	
	*	*	20-39	2.23	(1.54, 3.22)	
	*	*	≥40	3.32	(2.11, 5.22)	
HUMB	*	*	0	1.0		ns
(cig./day)	*	*	1-20	1.8	(0.6, 5.6)[5]	
	*	*	≥21	1.2	(0.3, 5.2)[5]	
INOU	*	*	0-4	1.00		<0.03
(cig./day)	*	*	5-19	1.58	(0.4, 5.7)[5]	
	*	*	≥20	3.09	(1.0, 11.8)[5]	
JANE[10]	*	*	0	1.00		*
(pack-yrs.)	*	*	1-24	0.71	(0.37, 1.55)	
	*	*	25-49	0.98	(0.47, 2.05)	
	*	*	≥50	1.10	(0.47, 2.56)	
KALA	26	46	0	1.00		0.08
(cig./day)	34	39	1-20	1.54	(0.88, 2.70)	
	22	22	21-40	1.77	(0.93, 3.35)	
	8	9	41+	1.57	(0.64, 3.85)	
KALA	26	46	0	1.00		0.04
(years)	15	21	<20	1.26	(0.56, 2.87)	
	15	20	20-29	1.33	(0.58, 3.03)	
	17	15	30-39	2.01	(0.86, 4.67)	
	17	16	≥40	1.88	(0.82, 4.33)	
KOO	32	67	0	1.00		0.16
(cig./day)	17	15	1-10	2.33	(0.9, 5.9)	
	25	35	11-20	1.74	(0.8, 3.8)	
	12	19	≥21	1.19	(0.5, 3.0)	
LAMT[6]	84	183	0	1.00		0.01
(cig./day)	22	22	1-10	2.18	(1.14, 4.15)	
	56	66	11-20	1.85	(1.19, 2.87)	
	20	21	≥21	2.07	(1.07, 4.03)	
LAMT[7]	53	92	0	1.00		0.01
(cig./day)	17	12	1-10	2.46	(1.09, 5.54)	
	37	28	11-20	2.29	(1.26, 4.16)	
	15	9	≥21	2.89	(1.18, 7.07)	

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Table 5-11. (continued)

Study	Case	Cont.	Exposure[1]	RR[2]	C.I.[2,3]	P-trend[4]
PERS[11]	34	*	0	1.0		0.12
(cig./day)	26	*	1-15	1.0	(0.6, 1.8)	
	7	*	≥16	3.2	(1.0, 9.5)	
TRIC[12]	24	109	0	1.00		0.01
(cig./day)	24	56	1-20	1.95	(1.13, 3.36)	
	14	25	≥21	2.55	(1.31, 4.93)	
WU[13]	*	*	0	1.0		*
(years	*	*	1-30	1.2	*	
exposed as	*	*	≥31	2.0	*	
adult)						
GARF(Coh)[14]	65	*	0	1.00		*
	39	*	1-19	1.27	(0.85, 1.89)	
(cig./day)	49	*	≥20	1.10	(0.77, 1.61)	
HIRA(Coh)[15]	37	21,895	0	1.00		0.01
	99	44,184	1-19[16]	1.41	(1.03, 1.94)	
(cig./day)	64	25,461	≥20	1.93	(1.35, 2.74)	

[1] Smoking by spouse unless otherwise specified.

[2] See footnote 6 in Table 5-10.

[3] Confidence intervals are 95% unless noted otherwise.

[4] P-value for upward trend. P-values from studies reporting only the significance level for trend were halved to reflect a one-sided alternative (i.e., upward trend). Values below 0.01 are shown as 0.01.

[5] 90% confidence interval.

[6] All histologies.

[7] Adenocarcinomas only.

[8] Years lived with a smoking husband.

[9] Neither crude data nor a test for trend is included in reference articles. The relative risk at each exposure category is significant alone, however, at $p < 0.05$.

[10] Data are from subject responses in Table 3 of the source.

[11] Low exposure level is for husband smoking up to 15 cigarettes per day or one pack (50 g) of pipe tobacco per week, or smoking any amount during less than 30 years of marriage. High exposure level is for husband smoking more than 15 cigarettes per day or one pack of pipe tobacco per week during 30 years of marriage or more.

[12] Data from Trichopoulos et al. (1983), with RRs corrected (personal communication from Trichopoulos, 1984).

[13] Years of exposure to spousal smoke *plus* years of exposure to workplace smoke; adenocarcinomas only.

[14] Value under "RR" is mortality ratio of observed to expected lung cancer deaths. Value under "Case" is number of observed lung cancer deaths.

[15] Standardized for age of subject (Hirayama, 1984). Values under "case" are numbers of lung cancer deaths; values under "cont." are total population.

[16] Includes former smokers of any exposure level.

*Data not available; ns = not significant.

Table 5-12. Reported p-values of trend tests for ETS exposure by study[1]

	Trend test results		
	Intensity (cig./day)	Duration (total years)	Cumulative (pack-years)[2]
AKIB	0.03	0.24	*
CORR	*	*	0.01
FONT	* *	0.07[3] <0.02[4]	0.04 <0.01
GAO	*	0.29	*
GARF	<0.02	*	*
GENG	<0.05[5]	<0.05[5]	*
HUMB	ns	*	*
INOU	<0.03	*	*
JANE	*[6]	*	*
KALA	0.08	0.04	*
KOO	0.16	*	*
LAMT	<0.01 <0.01[4]	*	*
PERS	0.12	*	*
TRIC	<0.01	*	*
WU	*	*[6]	*
GARF(Coh)	*[6]	*	*
HIRA(Coh)	<0.01	*	*

[1] Detailed data presented in Table 5-11.
[2] A "pack-year" is equivalent to one pack/day for 1 year.
[3] All cell types.
[4] Adenocarcinoma only.
[5] See footnote 9 in Table 5-11.
[6] Trend results presented without p-values or raw data--see Table 5-11.

*Data not available; ns = not significant.

tests for the various ETS exposure measures from the studies presented in Table 5-11. The exposure measure most commonly used was intensity of spousal smoking. Eight of the twelve studies that reported exposure-response data based on cigarettes per day showed statistical significance at the $p < 0.05$ level for the trend test. Again, the probability of this many statistically significant results occurring by chance in this number of studies is negligible ($p < 10^{-7}$). The trend test results for the other exposure measures were consistent, in general, with those based on cigarettes per day (three of six studies using total years of exposure were significant, as were two of two studies using pack-years).

Overall, 10 of the 14 studies with sufficient exposure-response data show statistically significant trends for one or more exposure measures. No possible confounder has been hypothesized that could explain the increasing incidence of lung cancer with increasing exposure to ETS in so many independent studies from different countries.

By country, the number of studies with significant results for upward trend is as follows: China, 1 of 2; Greece, 2 of 2; Hong Kong, 1 of 2; Japan, 3 of 3; Sweden, 0 of 1; and United States, 3 of 4. Of particular interest, two of the U.S. studies, GARF and CORR, are statistically significant for a test of trend, providing evidence for an association between ETS exposure and lung cancer even though neither was significant in a test for effect. In both cases, this occurs because the data supporting an increase in RR are largely at the highest exposure level. It appears that relatively high exposure levels are necessary to observe an effect in the United States, as would be expected if spousal smoking is a weaker surrogate for total ETS exposure in this country.

The U.S. study by Fontham et al. (1991), a well-conducted study and the largest case-control study of ETS and lung cancer to date, with the greatest power of all the U.S. studies to detect an effect, was statistically significant with a p-value of 0.04 for the trend test with pack-years as the exposure measure. When the analysis was restricted to adenocarcinomas (the majority of the cases), tests for trend were statistically significant by both years ($p = 0.02$) and pack-years ($p = 0.01$).

5.3.4. Conclusions

Two types of tests have been conducted: (1) a test for effect, wherein subjects must be classified as exposed or unexposed to ETS, generally according to whether the husband is a smoker or not, and (2) a trend test, for which exposed subjects are further categorized by some level of exposure, such as the number of cigarettes smoked per day by the husband, duration of smoking, or total number of packs smoked. Results are summarized in Table 5-13, with countries in the same order as in Table 5-9. Studies are noted in boldface if the test of effect or the trend

Table 5-13. P-values of tests for effect and for trend by individual study[1]

Country	Study	Power	Test	P-value[2]
Greece	KALA	0.39	Effect Trend	0.02 0.04
Greece	TRIC	0.45	Effect Trend	<0.01 <0.01
Hong Kong	CHAN	0.43	Effect	>0.50
Hong Kong	KOO	0.43	Effect Trend	0.06 0.16
Hong Kong	LAMT	0.73	Effect Trend	<0.01 <0.01
Hong Kong	LAMW	0.39	Effect	<0.01
Japan	AKIB	0.42	Effect Trend	0.05 0.03
Japan	HIRA(Coh)	0.75	Effect Trend	0.04 <0.01
Japan	INOU	0.17	Effect Trend	0.07(0.05)[3] 0.03
Japan	SHIM	0.37	Effect	0.38
Japan	SOBU	0.66	Effect	0.01
United States	BROW	0.15	Effect	0.28
United States	BUFF	0.17	Effect	>0.50
United States	BUTL(Coh)	0.18	Effect	0.17
United States	CORR	0.22	Effect Trend	0.10(0.005)[3] 0.01
United States	FONT	0.93	Effect Trend	0.03[4] 0.04[4]
United States	GARF	0.60	Effect Trend	0.12(0.01)[3] <0.02
United States	GARF(Coh)	0.92	Effect	0.18

(continued on the following page)

Table 5-13. (continued)

Country	Study	Power	Test	P-value[2]
United States	HUMB	0.20	Effect Trend	0.10 ns
United States	JANE	0.44	Effect	>0.50
United States	KABA	0.17	Effect	>0.50
United States	WU	0.21	Effect	0.29
W. Europe				
Scotland	Hole(Coh)	0.09	Effect	0.26
England	LEE	0.20	Effect	0.50
Sweden	**PERS**	0.45	**Effect** Trend	0.27**(0.02)**[3] 0.12
Sweden	SVEN	0.24	Effect	0.31
China	**GAO**	0.66	**Effect** Trend	0.18**(0.02)**[3] 0.29
China	**GENG**	0.32	**Effect** **Trend**	**0.01** **<0.05**
China	LIU	0.18	Effect	>0.50
China	WUWI	0.89	Effect	>0.50

[1] Test for effect--H_0: no increase in lung cancer incidence in never-smokers exposed to spousal ETS; H_A: an increase. Test for trend--H_0: no increase in lung cancer incidence as exposure to spousal ETS increases; H_A: an increase. P-values less than 0.05 are in boldface.

[2] Smallest p-value is used when there is more than one test for trend; ns = not significant.

[3] P-value in parentheses applies to test for effect at highest exposure only (see text).

[4] For all cell types. P-values for adenocarcinoma alone were smaller.

test is significant at 0.05 (one-tailed) or if, as in PERS and GAO, only the odds ratio at the highest exposure is significant. In 8 of the 11 studies in Greece, Hong Kong, or Japan, at least one of the tests is significant at 0.05. For the United States and Western Europe, 4 of the 15 studies are significant at 0.05 for at least one test. For the studies within the first group of countries (Greece, Hong Kong, and Japan), the median power is 0.43, and only 1 of the 10 studies (10%) has power less than 0.25 (INOU). In contrast, the median power for the United States and Western Europe together is 0.21, and 10 of the 15 studies (67%) have power less than 0.25. In a small study, significance is meaningful, but nonsignificance is not very informative because there is little chance of detecting an effect when there is one. Consequently, there are several studies in the United States-Western Europe group that provide very little information. Two of the four studies in China are significant at the 0.05 level for at least one test. The two nonsignificant studies in China (LIU and WUWI) are not very informative on ETS for reasons previously described (see Section 5.3.2.1).

For the U.S. and Western Europe studies, 3 of the 5 with power greater than 0.25 are shown in boldface (FONT, GARF, and PERS), indicating at least suggestive evidence of an association between ETS and lung cancer, compared with only 1 of 10 with power under 0.25 (CORR). All three of the higher power studies are significant for effect (PERS and GARF are significant at the highest exposure only) and two (FONT and GARF) are also significant for trend. CORR is significant for trend and for effect at the highest exposure level. Overall, the evidence of an association in the United States and Western Europe is strengthened by the tests at the highest exposure levels and by the tests for trend.

To summarize, the results of the several different analyses in this section provide substantial evidence that exposure to ETS from spousal smoking is associated with increased lung cancer mortality. The evidence is strongest in Greece, Hong Kong, Japan, and the United States. The evidence for Western Europe appears similar to that in the United States, but there are far fewer studies. (The usefulness of statistical information from studies in China is quite limited, so no conclusions are drawn from the studies there.)

The evidence from the individual studies, without pooling within each country, is also conclusive of an association. Adjustment, on an individual study basis, for potential bias due to smoker misclassification results in slightly lower relative risk estimates but does not affect the overall conclusions. The results based on either the test for effect or the test for trend cannot be attributed to chance alone. Tests for effect, tests at the highest exposure levels, and tests for trend jointly support the conclusion of an association between ETS and lung cancer in never-smokers.

5.4. STUDY RESULTS ON FACTORS THAT MAY AFFECT LUNG CANCER RISK

5.4.1. Introduction

The possibility of chance accounting for the observed associations between ETS and lung cancer has been virtually ruled out by the statistical methods previously applied. Potential sources of bias and confounding must still be considered to determine whether they can explain the observed increases. While the exposure-response relationships reviewed in Section 5.3.3.3 generally reduce the likelihood of bias and confounding accounting for the observed associations, this section focuses on specific factors that may bias or modify the lung cancer results.

Validity is the most relevant concern for hazard identification. Generalizability of results to the national population (depending on "representativeness" of the sample population, treated in the text) is important for the characterization of population risk, but no more so than validity. As stated by Breslow and Day (1980), "In an analysis, the basic questions to consider are the degree of association between risk for disease and the factors under study, the extent to which the observed associations may result from bias, confounding and/or chance, and the extent to which they may be described as causal."

Whereas Section 5.3 examined the epidemiologic data by individual study and by pooling results by country, this section considers potential sources of bias and confounding and their implications for interpretation of study results. As indicated in the brief review of the meanings of bias and confounding at the end of this section, confounding arises from the characteristics of the sample population, whereas bias is the result of individual study features involving design, data collection, or data analysis. Section 5.4.2 briefly reviews the evidence on non-ETS risk factors and modifiers of lung cancer incidence that appears in the 30 epidemiologic studies (not counting KATA) reviewed for this report. None of the factors has been established as a confounder of ETS, which would require demonstrating that the factor causes lung cancer and is correlated with ETS exposure (specifically, spousal smoking to affect the analysis in this report).

Our objective is to consider the influence of sources of uncertainty on the statistical measures summarized in Table 5-13, although there are limitations to such an endeavor. For example, not controlling for a factor such as age in the statistical analysis, which should be done whether or not the study design is matched on age, may require reanalyzing data not included in the study report. Potential sources of bias are just that--*potential*--and their actual effect may be impossible to evaluate (e.g., selection bias in case-control studies). Although numerous questions of interest cannot be answered unequivocally, or even without a measure of subjective judgment, it is nevertheless worthwhile to consider issues that may affect interpretation of the quantitative results. The issues of concern are largely those of epidemiologic investigations in general that motivate the conscientious investigator to implement sound methodology. Statistical uncertainty aside, the outcomes of studies that fare well under close examination inspire more confidence and thus deserve greater emphasis than those that do poorly.

Preliminary to the next sections, some relevant notes on epidemiologic concepts are excerpted from two IARC volumes entitled *Statistical Methods in Cancer Research* (Breslow and Day, 1980, 1987), dealing with case-control and cohort studies, respectively, which are excellent references. In the interest of brevity, an assortment of relevant passages is simply quoted directly from several locations in the references (page numbers and quotation marks have been omitted to improve readability). Some readers may wish to skip to the next section; those interested in a more fluid, cogent, and thorough presentation are referred to the references.

- Bias and confounding. The concepts of bias and confounding are most easily understood in the context of cohort studies, and how case-control studies relate to them. Confounding is intimately connected to the concept of causality. In a cohort study, if some exposure E is associated with disease status, then the incidence of the disease varies among the strata defined by different levels of E. If these differences in incidence are caused (partially) by some other factor C, then we say that C has (partially) confounded the association between E and the disease. If C is not causally related to disease, then the differences in incidence cannot be caused by C, thus C does not confound the disease/exposure association.

  Confounding in a case-control study has the same basis as in a cohort study . . . and cannot normally be removed by appropriate study design alone. An essential part of the analysis is an examination of possible confounding effects and how they may be controlled.

  Bias in a case-control study, by contrast, [generally] arises from the differences in design between case-control and cohort studies. In a cohort study, information is obtained on exposures before disease status is determined, and all cases of disease arising in a given time period should be ascertained. Information on exposure from cases and controls is therefore comparable, and unbiased estimates of the incidence rates in the different subpopulations can be constructed. In case-control studies, however, information on exposure is normally obtained after disease status is established, and the cases and controls represent samples from the total. Biased estimates of incidence ratios will result if the selection processes leading to inclusion of cases and controls in the study are different (selection bias) or if exposure information is not obtained in a comparable manner from the two groups, for example, because of differences in response to a questionnaire (recall bias). Bias is thus a consequence of the study design, and the design should be directed towards eliminating it. The effects of bias are often difficult to control in the analysis, although they will sometimes resemble confounding effects and can be treated accordingly.

  To summarize, confounding reflects the causal association between variables in the population under study, and will manifest itself similarly in both cohort and case-control studies. Bias, by contrast, is not a property of the underlying population. It results from inadequacies in the design of case-control studies, either in the selection of cases or controls or from the manner in which the data are acquired.

- On prospective cohort studies. One of the advantages of cohort studies over case-control studies is that information on exposure is obtained before disease status is ascertained. One can therefore have considerable confidence that errors in measurement are the same for individuals who become cases of the disease of interest, and the remainder of the cohort. The complexities possible in retrospective case-control studies because of differences in recall between cases and controls do not apply. [Regarding the success of a cohort study, the] follow-up over time . . . is the essential feature. . . . The success with which the follow-up is achieved is probably the basic measure of the quality of the study. If a substantial proportion of the cohort

> is lost to follow-up, the validity of the study's conclusions is seriously called into question.

- On case-control studies. Despite its practicality, the case-control study is not simplistic and it cannot be done well without considerable planning. Indeed, a case-control study is perhaps the most challenging to design and conduct in such a way that bias is avoided. Our limited understanding of this difficult study design and its many subtleties should serve as a warning--these studies must be designed and analyzed carefully with a thorough appreciation of their difficulties. This warning should also be heeded by the many critics of the case-control design. General criticisms of the design itself too often reflect a lack of appreciation of the same complexities which make these studies difficult to perform properly.

  The two major areas where a case-control study presents difficulties are in the selection of a control group, and in dealing with confounding and interaction as part of the analysis. . . these studies are highly susceptible to bias, especially selection bias which creates non-comparability between cases and controls. The problem of selection bias is the most serious potential problem in case-control studies. . . . Other kinds of bias, especially that resulting from non-comparable information from cases and controls are also potentially serious; the most common of these is recall . . . bias which may result because cases tend to consider more carefully than do controls the questions they are asked or because the cases have been considering what might have caused their cancer.

In addition to standard demographic factors (e.g., age) that are usually controlled for in a study, a number of other variables have been considered as potential risk factors (including risk modifiers) for lung cancer. If a factor increases the risk of lung cancer and its presence is correlated with exposure to spousal ETS, then it could be a confounder of ETS if not controlled for in a study's analysis. In general, factors that may affect risk of lung cancer and also may be correlated with ETS exposure are of interest as possible explanatory variables. Findings from the ETS studies are reviewed for six general categories: (1) personal history of lung disease, (2) family history of lung disease, (3) heat sources, (4) cooking with oil, (5) occupation, and (6) diet. Table 5-14 provides an overview of results in these categories. Two shortcomings are common in the studies where these factors appear: failure to evaluate the correlation of exposure to the factor and to ETS, and then to adjust the analysis accordingly; and failure to adjust significance levels for multiple comparisons. Multiple tests on the same data increase the chance of a false positive (i.e., outcomes appear to be more significant than warranted due to the multiple comparisons being made on the same data).

5.4.2. History of Lung Disease

Results regarding history of lung disease have been reported in eight of the reviewed ETS studies, but with little consistency. Tuberculosis (TB), for example, is significantly associated with lung cancer in GAO (OR = 1.7; 95% C.I. = 1.1, 2.4) but not in SHIM (OR = 1.1, no other

Table 5-14. Other risk-related factors for lung cancer evaluated in selected studies

Category	Possible risk factor	Mixed outcome	No evidence
Personal or family history	WU (US) GENG (Ch) LIU (Ch)	SHIM (Jap) GAO (Ch)	
Heat source for cooking or heating	WU (US) WUWI (Ch) GENG (Ch) GAO (Ch) LIU (Ch)	SOBU (Jap)	LAMW (HK)
Cooking with oil	WUWI (Ch) GAO (Ch)		
Diet	WU (US)	KALA (Gr) HIRA (Jap)	SHIM (Jap)
β-carotene			WUWI (Ch) KALA (Gr) GAO (Ch)-harmful
Occupation	WUWI (Ch) SHIM (Jap) GENG (Ch) BUTL (US) BUFF (US)		WU (US) GAO (Ch)

statistics), LIU or WU (no ORs provided). Chronic bronchitis, on the other hand, is nonsignificant in GAO (OR = 1.2; 95% C.I. = 0.8, 1.7), SHIM (OR = 0.8), KABA, and WU, but it is highly significant in LIU (OR = 7.37; 95% C.I. = 2.40, 22.66 for females; OR = 7.32; 95% C.I. = 2.66, 20.18 for males) and mildly so in WUWI (OR = 1.4; 95% C.I. = 1.2, 1.8). (Notably, the populations of WUWI, LIU, and GENG were exposed to non-ETS sources of household smoke.) Consideration of each lung disease separately, as presented, ignores the effect of multiple comparisons described above. For example, GAO looked at five categories of lung disease. If that were taken into account, TB would no longer be significant. No discussion of the multiple comparisons effect was found in any of the references, which might at least be acknowledged.

Broadening our focus to examine the relationship of lung cancer to history of lung disease in general does little to improve consistency. GENG reports an adjusted OR of 2.12 (95% C.I. = 1.23, 3.63) for history of lung disease, GAO's disease-specific findings are consistently positive, and WUWI reports three positive associations out of an unknown number assessed. SHIM and

WU, however, consistently found no effect except marginally for silicosis (perhaps better construed as an occupational exposure surrogate) in SHIM and for childhood pneumonia in WU. LIU found a significant association only for chronic bronchitis and KABA only for pneumonia. Interpretation is hampered by the lack of numerical data for factors that were not statistically significant in KABA, LIU, and WU. Even with such data, however, interpretation is hampered by the absence of control for key potential confounders in many of the studies (e.g., age in GENG and LIU). Only one study (WU) attempted to control for a history variable (childhood pneumonia), which reportedly did not alter the ETS results. The importance of prior lung disease as a factor in studies of ETS is thus unclear, but it does not appear to distort results one way or the other.

5.4.3. Family History of Lung Disease

Only a few of the studies addressed family history of lung disease. GAO found no significant association between family history of lung cancer and subjects' disease status (e.g., parental lung cancer OR = 1.1; 95% C.I. = 0.6, 2.3), and positive family histories were very rare (e.g., 1.0% among mothers of either cases or controls). In contrast, WUWI reports a significant association with history of lung cancer in first-degree relatives (OR = 1.8; 95% C.I. = 1.1, 3.0), which occurred in about 4.5% of the cases. The presence of TB in a household member (OR = 1.6; 95% C.I. = 1.2, 2.1) is also significant, even after adjustment for personal smoking and TB status. The rarity of family-linked lung cancer in these populations makes accurate assessment difficult and also reduces the potential impact on results of any effect it may have. Its study in populations where such cancer is more common would be more appropriate. The household TB outcome may be the result of multiple comparisons and/or confounding, particularly in view of the weaker (nonsignificant) outcome noted for *personal* TB status.

5.4.4. Heat Sources for Cooking or Heating

Household heating and cooking technologies have received considerable attention as potential lung cancer risk factors in Asian ETS studies. Most studies have focused on fuel type. Kerosene was specifically examined in three studies. All three found positive associations--CHAN and LAMW for kerosene cooking, and SHIM for kerosene heating--but none of the associations were statistically significant, and the SHIM relationship held only for adult and not for childhood exposure. Five studies specifically examined coal. GENG evaluated use of coal for cooking and found a significant positive association. Use of coal for household cooking or heating prior to adulthood is significantly associated with lung cancer in WU's study of U.S. residents, but no results for adulthood are mentioned. Recent charcoal stove use showed a positive (OR = 1.7) but not significant association in SHIM. Separate analyses of five coal-burning devices and two non-coal-burning devices by WUWI found positive although not always significant associations for the coal burners. In contrast, SOBU found no association between use of unventilated heating devices--including mostly kerosene and coal-fueled types but also some wood and gas burners--and lung cancer (OR = 0.94 for use at age 15, 1.09 at age 30, 1.07 at present). Results for wood or straw cooking were specifically reported in three studies. SOBU found a significant association for use of wood or straw at age 30 (OR = 1.89; 95% C.I. = 1.16, 3.06) but only a weak relationship at age 15. GAO found no association with current use of wood for cooking (OR = 1.0; 95% C.I. = 0.6, 1.8), and WUWI mentions that years of household heating with wood, central heating, and coal showed nonsignificant trends (negative, negative, and positive, respectively).

Overall, studies that examined heating and cooking fuels generally found evidence of an association with lung cancer for at least one fuel, which was usually but not always statistically significant. Such relationships appeared most consistently for use of coal and most prominently in WUWI and LIU. Neither study found a significant association between ETS and lung cancer, nor did either address whether coal use was associated with ETS exposure. The presence of non-ETS sources of smoke within households, however, may effectively mask detection of any effect due to ETS (as noted by the authors of WUWI). Evidence of effects of other fuel types and devices is more difficult to evaluate, particularly because many studies do not report results for these factors, but kerosene-fueled devices seem worthy of further investigation.

5.4.5. Cooking With Oil

Cooking with oil was examined by GAO and WUWI, both conducted in China, with positive associations for deep-frying (OR ranges of 1.5-1.9 and 1.2-2.1, respectively, both increasing with frequency of cooking with oil). GAO also reports positive findings for stir-frying, boiling (which in this population often entails addition of oil to the water), and smokiness during cooking and found that most of these effects seemed specific for users of rapeseed oil. These results may apply to other populations where stir-frying and certain other methods of cooking with oil are common. Neither study, however, addressed whether use of cooking with oil is correlated with ETS exposure.

5.4.6. Occupation

Seven studies investigated selected occupational factors, with five reporting positive outcomes for one or more occupational variables. The outcomes, however, are somewhat inconsistent. SHIM found a strong and significant relationship with occupational metal exposure

(OR = 4.8) and a nonsignificant one with coal, stone, cement, asbestos, or ceramic exposure, while WUWI found significant positive relationships for metal smelters (OR = 1.5), occupational coal dust (OR = 1.5), and fuel smoke (OR = 1.6) exposure. Textile work is positively associated with lung cancer in KABA and negatively associated with lung cancer in WUWI. BUFF divided occupations into nine categories plus housewife and found eight positive and one negative associations relative to housewives, but only one ("clerical") is significant. GAO, on the other hand, found no association with any of six occupational categories, while GENG found a significant association for an occupational exposure variable that encompassed textiles, asbestos, benzene, and unnamed other substances (OR = 3.1; 95% C.I. = 1.58, 6.02). WU reported "no association between any occupation or occupational category," although there was a nonsignificant excess among cooks and beauticians. Finally, BUTL(Coh) found an increased RR for wives whose husbands worked in blue collar jobs (> 4; never-smoker). HIRA(Coh) did not present findings for husband's occupation as a risk factor independently but reported that adjustment for this factor did not alter the study's ETS results. Few studies attempted to adjust ETS findings for occupational factors--SHIM found only modest effects of such adjustment for occupational metal exposure, despite an apparent strong independent effect for this factor, and GENG found only minimal effect of occupational exposure on active smoking results but did no adjustment of ETS results. Overall, multiple comparisons, other factors (e.g., socioeconomic status, age), and the rarity of most specific occupational exposure sources probably account for the inconsistent role of occupation in these studies.

5.4.7. Dietary Factors

Investigations related to diet have been reported in nine of the ETS studies, with mixed outcomes. The fundamental difficulty lies in obtaining accurate individual values for key nutrients of interest, such as β-carotene. The relatively modest size of most ETS study populations adds further uncertainty in attempts to detect and assess any dietary effect that, if present, is likely to be small. In those studies where dietary data were collected and adjusted for in the analysis of ETS, diet has had no significant effect. Nevertheless, diet has received attention in the literature as a possible explanatory factor in the observed association between ETS exposure and lung cancer occurrence (e.g., Koo, 1988; Koo et al., 1988; Sidney et al., 1989; Butler, 1990, 1991; Marchand et al., 1991); therefore, a more detailed and specific discussion is provided in this section.

Diet is of interest for a potential protective effect against lung cancer. If nonsmokers unexposed to passive smoke have a lower incidence of spontaneous (unrelated to tobacco smoke) lung cancer incidence due to a protective diet, then the effect would be upward bias in the RR for

ETS. However, for diet to *explain* fully the significant association of ETS exposure in Greece, Hong Kong, Japan, and the United States, which differ by diet as well as other lifestyle characteristics, it would need to be shown that in *each* country: (1) there is a diet protective against lung cancer from ETS exposure, (2) diet is inversely associated with ETS exposure, and (3) the association is strong enough to produce the observed relationship between ETS and lung cancer. Diet may modify the magnitude of any lung cancer risk from ETS (conceivably increase or decrease risk, depending on dietary components), but that would not affect whether ETS is a lung carcinogen.

The literature on the effect of diet on lung cancer is not consistent or conclusive, but taken altogether there may be a protective effect from a diet high in β-carotene, vegetables, and possibly fruits. Also, there is some evidence that low consumption of these substances may correlate with increased ETS exposure, although not necessarily for all study areas. The calculations made by Marchand et al. (1991) and Butler (1990, 1991) are largely conjectural, being based only on *assumed* data. Therefore, we examined the passive smoking studies themselves for empirical evidence on the effect of diet and whether it may affect ETS results.

It was found that nine of the studies have data on diet, although only five of them use a form of analysis that assesses the impact of diet on the ETS association. None of those five studies--CORR, HIRA(Coh), KALA, SHIM, and SVEN--found that diet made a significant difference. In the four studies where data on diet were collected but not controlled for in the analysis of ETS, three (GAO, KOO, and WUWI) are from East Asia and one (WU) is from the United States. Koo (1988), who found strong protective effects for a number of foods, has been one of the main proponents of the idea that diet may explain the passive smoking lung cancer effect. To our knowledge, however, she has not published a calculation examining that conjecture in her own study where data were collected on ETS subjects. In WU, a protective effect of β-carotene was found, but the data include a high percentage of smokers (80% of the cases for adenocarcinoma, 86% for squamous cell), and the number of never-smokers is small. In recent correspondence concerning the large FONT study, its authors state that "mean daily intake of beta-carotene does not significantly differ between study subjects whose spouse smoked and those whose spouse never smoked" (Fontham et al., 1992).

The equivocal state of the literature regarding the effect of diet on lung cancer is also apparent in the nine ETS studies that include dietary factors, summarized in Table 5-15. Note that GAO found an adverse effect from β-carotene. HIRA and KOO found opposite effects from fish while SHIM found no effect. Fruit was found to be protective by KALA and KOO but adverse by SHIM and WUWI. Retinol (based on consumption of eggs and dairy products) was found to be protective by KOO but adverse by GAO and WUWI.

Table 5-15. Dietary effects in passive smoking studies of lung cancer in females

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc.				Remarks
			Lowest	Next	Next	Highest	
CORR[2]	2.07	Carotene	No data given				Never-smokers. Carotene and total vitamin A were examined. "Except for gender, age, and study area, no confounding was detected."
		Vitamin A	No data given				
GAO	1.19	Carotene rich	1.0	1.0	1.3	2.0[3]	Patterns were similar for smokers and nonsmokers. Passive RR was not adjusted for diet, possibly because the trends were the opposite of those in the literature.
		Retinol rich	1.0	1.1	1.0	1.1	
		Vitamin A index	1.0	1.6[3]	1.2	2.0[3]	
HIRA[4]	1.53	Green-yellow veg.	-	1.0[5]	-	0.86[6]	Never-smokers. Lung cancer risks for wives whose husbands were former smokers plus 1-19 cig./day smokers and 20+ cig./day smokers relative to never-smokers were 1.50 and 1.79 when adjusted for wives' age (Hirayama, 1984). They ranged from 1.53 to 1.69 and 1.66 to 1.91 when adjusted for wives' age, husband's occupation, and each of the various dietary factors.
		Fish	-	1.0	-	1.87[3]	
		Meat	-	1.0	-	0.62	
		Milk	-	1.0	-	1.30	
		Soy paste soup	-	1.0	-	0.93	
KALA	1.92	β-carotene	1.0	-	-	1.01	Never-smokers. Controlled for age, years of schooling, interviewer, and total energy intake. No confounding was observed between the passive smoking effect and the effect of fruits, or between that of fruits and that of vegetables. Passive risk increased to 2.11 when adjusted for fruit consumption.
		Vegetables	1.0	-	-	1.09	
		Fruits	1.0	-	-	0.33[3]	
		Vitamin C	1.0	-	-	0.67	
		Retinol (preformed)	1.0	-	-	1.31	

(continued on the following page)

Table 5-15. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc. Lowest	Next	Next	Highest	Remarks
KOO[7]	1.55	Leafy green veg.	-	1.0	0.49	0.49	Never-smokers. Values are adjusted for age, numbers of live births, and schooling. Diet items are selected to compare with those in other studies. No calculation is shown of confounding effect of diet on the passive smoking risk either in Koo et al. (1987), Koo (1988), Koo et al. (1988), or Koo (1989). Fresh fruit, vitamin C, fresh fish, and retinol showed statistically significant trends.
		Carrots	-	1.0	1.31	0.51	
		β-carotene	-	1.0	0.73	0.73	
		Fresh fruit	-	1.0	0.81	0.42	
		Vitamin C	-	1.0	0.55	0.47	
		Fresh fish	-	1.0	0.46	0.35	
		Smoked/cured meat/poultry	-	1.0	0.82	0.92	
		Milk	-	1.0	1.66	0.92	
		Retinol	-	1.0	0.55	0.42	
SHIM	1.08	Green-yellow veg.	-	1.0[8]	-	0.9[8]	Never-smokers. No dose response was found. No difference between cases and controls was found regarding intake of green-yellow vegetables.
		Fruit	-	1.0	-	1.2	
		Milk	-	1.0	-	1.0	
		Fish, pork, or lamb	-	1.0	-	1.0	
		Chicken	-	1.0	-	0.7	
SVEN	1.26	Carrots	1.0[9]	0.7[10]	-	0.6[3,11]	Adjusted for age, smoking, cumulative Rn exposure and municipality. The inclusion of carrot consumption in the regression model "had only a slight effect on the risk estimates of the other exposure variables." See Svensson (1988).

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Table 5-15. (continued)

Study	Passive[1] RR	Diet entity	Lung cancer relative risk by dietary intake quartile, tertile, etc.				Remarks
			Lowest	Next	Next	Highest	
WU	1.41	β-carotene	1.0	0.52	0.32	0.40[3]	For adenocarcinoma. Risks of 0.67, 1.0, and 0.63, high calf versus low calf, were observed for β-carotene, preformed vitamin A, and dairy and eggs for squamous cell carcinoma. Adjusted for cigarettes smoked per day. No adjustment is shown to the passive risk for diet.
		Preformed Vit. A	1.0	0.92	0.50	0.83	
		Dairy products and eggs	1.0	0.82	0.63[3]	0.37[3]	
WUWI	0.79	Vegetables					Adjusted for age, education, personal smoking, and study area. Eight variables other than smoking were thought to have a significant effect on lung cancer risk. Diet variables were not included in this list, and no adjustment to the passive risk was made for them.
		high-carotene	1.0	1.1	1.0	0.9	
		low-carotene	1.0	1.0	1.0	0.8	
		Fresh fruit	1.0	1.0	1.4[3]	1.5[3]	
		Animal protein	1.0	1.6[3]	1.6[3]	2.3[3]	

[1] From Table 5-5.

[2] As reanalyzed by Dalager et al. (1986).

[3] Statistically significant at the p = 0.05 level.

[4] Case-control study nested in Hirayama's cohort study, ages 40-69 only (Hirayama, 1989).

[5] Less than daily.

[6] Daily.

[7] From Koo (1988).

[8] Cutoffs various.

[9] Less than once per week.

[10] Once per week.

[11] More than once per week.

In view of the results summarized in Tables 5-14 and 5-15, the actual data of ETS studies do not support the suspicion that diet introduces a systematic bias in the ETS results. Indeed, it would be difficult to show otherwise. Dietary intake is difficult to assess; dietary habits vary within countries and enormously between countries, making it difficult to attribute any effect on lung cancer to a particular food group; lifestyle characteristics and consumption of food and beverage with possibly an adverse effect may be associated, either positively or negatively, with the food group under consideration. It would, of course, be helpful to identify dietary factors that may affect lung cancer, positively or negatively, because that information could usefully contribute to public health. To affect interpretation of ETS results, however, it would need to be established also that consumption of the dietary factor of interest is highly correlated with ETS exposure in study populations where ETS exposure is linked with increased incidence of lung cancer.

5.4.8. Summary on Potential Modifying Factors

In summary, an examination of six non-ETS factors that may affect lung cancer risk finds none that explains the association between lung cancer and ETS exposure as observed by independent investigators across several countries that vary in social and cultural behavior, diet, and other characteristics. On the other hand, the high levels of indoor air pollution from other sources (e.g., smoky coal) that occur in some parts of China and show statistical associations with lung cancer in the studies of GENG, LIU, and WUWI may mask any ETS effects in those studies.

5.5. ANALYSIS BY TIER AND COUNTRY

In this section, attention is directed to properties of individual studies, including potential sources of bias, that may affect their utility for the assessment of ETS and lung cancer. Studies are assessed based on qualitative as well as statistical evaluation. The studies are qualitatively reviewed in Appendix A and categorized into "tiers" within country. Studies are individually scored according to items in eight categories. Study scores are then implemented in a numerical scheme to classify each study into one of four tiers according to that study's assessed utility for hazard identification of ETS. Tier 1 studies are those of greatest utility for investigating a potential association between ETS and lung cancer. Other studies are assigned to Tiers 2, 3, and 4 as confidence in their utility diminishes. Tier 4 is reserved for studies we would exclude from analysis for ETS, for various reasons specified in the text. In the statistical analysis presented in this section, the summary RR for each country is recalculated for studies in Tier 1 alone and for Tiers 1-2, 1-3, and 1-4 (the last category corresponds to the combined analysis shown in

Table 5-9) by country. This exercise provides some idea of the extent to which the summary RR for a country depends on the choice of studies.

The assignment of studies to tiers is shown in Table 5-16. Overall, 5 studies are in the highest tier, while 15, 5, and 5 studies are in Tiers 2, 3, and 4, respectively (KATA was not assigned to a tier). Studies in Tier 4 are not recommended for the objectives of this report. The statistical weight for Tiers 1, 2, and 3 pooled together for each country is shown in Table 5-9 as a percentage of the total for corresponding tiers over all countries. Emphasis on studies through Tier 2 or through Tier 3 is somewhat arbitrary. Although studies in Tier 1 are judged to be of the highest utility, exclusive attention to Tier 1 would eliminate considerable epidemiologic data because only 16% of the studies are in Tier 1. Excluding Tier 4 leaves the choices to either all studies through Tier 2 or through Tier 3. GAO is the only study in China that was not placed in Tier 4, but there is little basis to assume that this single study from Shanghai should be representative of a vast country like China.

Table 5-17 presents adjusted relative risk estimates, 90% confidence intervals, and significance levels (one-sided) from studies pooled by country and by tier. The pooled relative risks do not decrease as the results from studies in Tier 2 and Tier 3 are combined with those from Tier 1, with two exceptions: In the United States, the pooled estimate changes from 1.28 to 1.22 to 1.19 when Tier 2 and Tier 3 studies are added, respectively, and in Western Europe, the pooled estimate changes from 1.21 to 1.17 when Tier 2 studies are added. The pooled estimates for studies through Tier 2 are statistically significant at $p = 0.02$ (one-tailed) in Greece, Hong Kong, Japan, and the United States; Western Europe is the exception ($p = 0.22$). The same statement holds with Tier 2 replaced by Tier 3, except that China includes one study at $p = 0.18$. The relative risk results from all four Western European studies (RR = 1.17) is virtually the same for all U.S. studies (RR = 1.19), but with less power that value is not significant for Western Europe. The similarity of outcomes is also interesting, however, because Western Europe is probably more similar to the United States than the other countries.

Analysis by tiers provides a methodology for weighting studies according to their utility for hazard identification of ETS. It allows one to emphasize those studies thought to provide better data for analysis of an ETS effect. The addition of studies of lower utility to the analysis, such as inclusion of Tier 3 studies with those from Tiers 1 and 2, has a small effect on the relative risk estimate but both increases its statistical significance and narrows its confidence interval. In view of that outcome and the results and discussion in Section 5.4, this analysis finds little to indicate confounding or bias in studies through Tier 3 (which include all studies in the United States). In summary, it is concluded that the association of ETS and lung cancer observed from

Table 5-16. Classification of studies by tier

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
Greece	KALA	X			
Greece	TRIC			X	
Hong Kong	KOO	X			
Hong Kong	LAMT		X		
Hong Kong	LAMW			X	
Hong Kong	CHAN				X
Japan	AKIB		X		
Japan	HIRA(Coh)		X		
Japan	SHIM		X		
Japan	SOBU		X		
Japan	INOU				X
United States	FONT	X			
United States	BUTL(Coh)		X		
United States	GARF		X		
United States	HUMB		X		
United States	JANE		X		
United States	WU		X		
United States	BROW		X		
United States	BUFF			X	
United States	CORR		X		
United States	GARF(Coh)			X	
United States	KABA		X		

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Table 5-16. (continued)

Country	Study	Tier 1	Tier 2	Tier 3	Tier 4
W. Europe					
Scotland	HOLE(Coh)	X			
Sweden	PERS	X			
Sweden	SVEN		X		
England	LEE		X		
China	GAO			X	
China	GENG				X
China	LIU				X
China	WUWI				X

the analysis of 30 epidemiologic studies in eight different countries is not due to chance alone and is not attributable to bias or confounding.

5.6. CONCLUSIONS FOR HAZARD IDENTIFICATION

5.6.1. Criteria for Causality

According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria [that] must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance."

As demonstrated in the preceding sections, the overall results observed in the 30 epidemiologic studies are not attributable to chance and the association between ETS and lung cancer is not explained by bias or confounding.

Table 5-17. Summary data interpretation by tiers within country[1]

Through Tier[2]	Relative weight[3] (%)	Country[4]	Studies added	RR	Confidence interval 90%	P-value effect
1		Greece	KALA	1.92	(1.13, 3.23)	0.02
2	**4**	**Greece**	**---**	**1.92**	**(1.13, 3.23)**	**0.02**
3	**6**	**Greece**	**TRIC**	**2.01**	**(1.42, 2.84)**	**0.0005**
4		Greece	---	2.01	(1.42, 2.84)	0.0005
1		Hong Kong	KOO	1.54	(0.98, 2.43)	0.06
2	**16**	**Hong Kong**	**LAMT**	**1.61**	**(1.25, 2.07)**	**0.0009**
3	**14**	**Hong Kong**	**LAMW**	**1.75**	**(1.39, 2.19)**	**0.00002**
4		Hong Kong	CHAN	1.48	(1.21, 1.81)	0.0008
1		Japan	---	---	---	---
2	**30**	**Japan**	**AKIB, HIRA(Coh), SHIM, SOBU**	**1.39**	**(1.16, 1.66)**	**0.001**
3	**23**	**Japan**	**---**	**1.39**	**(1.16, 1.66)**	**0.001**
4		Japan	INOU	1.41	(1.18, 1.69)	0.0007
1		United States	FONT	1.28	(1.03, 1.60)	0.03
2	**41**	**United States**	**BUTL(Coh), CORR, GARF, HUMB, JANE, KABA, WU**	**1.22**	**(1.04, 1.42)**	**0.02**
3	**43**	**United States**	**BROW, BUFF, GARF(Coh)**	**1.19**	**(1.04, 1.35)**	**0.02**
4		United States	---	1.19	(1.04, 1.35)	0.02
1		W. Europe	HOLE(Coh), PERS	1.21	(0.79, 1.90)	0.24
2	**9**	**W. Europe**	**SVEN, LEE**	**1.17**	**(0.85, 1.64)**	**0.22**
3	**7**	**W. Europe**	**---**	**1.17**	**(0.85, 1.64)**	**0.22**
4		W. Europe	---	1.17	(0.85, 1.64)	0.22
1		China	---	---	---	---
2	**0**	**China**	**---**	**---**	**---**	**---**
3	**7**	**China**	**GAO**	**1.19**	**(0.87, 1.62)**	**0.18**
4		China	GENG, LIU, WUWI	0.95	(0.81, 1.12)	0.70

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Table 5-17. (continued)

[1] Use of Tiers 1 through 2 or Tiers 1 through 3, both shown in boldface, is recommended. Tier 4 is *not* recommended.
[2] Each line contains the studies in the previous tiers plus those added.
[3] Percentage of total weight by country for Tiers 1 through 2 or 1 through 3.
[4] Western Europe consists of England, Scotland, and Sweden.

Below, the evidence for a causal association between ETS and lung cancer is evaluated according to seven specific criteria for causality developed by an EPA workshop to supplement the *Guidelines* (U.S. EPA, 1989). These criteria are similar to the original and classical recommendations of Hill (1953, 1965). The seven recommended (but not official) criteria from the EPA workshop, which vary between essential and desirable, are listed below (U.S. EPA, 1989).

> A causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of these actually establishes causality; actual proof is rarely attainable when dealing with environmental carcinogens. The absence of any one or even several of the others does not prevent a causal interpretation. Only the first criterion (temporal relationship) is essential to a causal relationship: with that exception, none of the criteria should be considered as either necessary or sufficient in itself. The first six criteria apply to an individual study. The last criterion (coherence) applies to a consideration of all evidence in the entire body of knowledge.
>
> 1. Temporal relationship: The disease occurs within a biologically reasonable timeframe after the initial exposure to account for the specific health effect.
>
> 2. Consistency: When compared to several independent studies of a similar exposure in different populations, the study in question demonstrates a similar association which persists despite differing circumstances. This usually constitutes strong evidence for a causal interpretation (assuming the same bias or confounding is not also duplicated across studies).
>
> 3. Strength of association: The greater the estimate of risk and the more precise, the more credible the causal association.
>
> 4. Dose-response or biologic gradient: An increase in the measure of effect is correlated positively with an increase in the exposure or estimated dose. If present, this characteristic should be weighted heavily in considering causality. However, the absence of a dose-response relationship should not be construed by itself as evidence of a lack of a causal relationship.
>
> 5. Specificity of the association: In the study in question, if a single exposure is associated with an excess risk of one or more cancers also found in other studies, it increases the likelihood of a causal interpretation.
>
> 6. Biological plausibility: The association makes sense in terms of biological knowledge. Information from toxicology, pharmacokinetics, genotoxicity, and in vitro studies should be considered.
>
> 7. Coherence: Coherence exists when a cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the disease. A proposed association that conflicted with existing knowledge would have to be examined with particular care. (This criterion has been called "collateral evidence" previously.)

5.6.2. Assessment of Causality

We consider the extent to which the criteria for causality are satisfied for the ETS studies. Regarding *temporal relationship*, ETS exposure classification is typically based on the marital history of a subject, which varies, or on the status at the beginning of a prospective cohort study. Very few studies up through Tier 3 considered current exposure status only (see Appendix A), so some history of ETS exposure is largely the rule for ETS-exposed subjects. Analysis of data by exposure level in Section 5.3.3 indicates increased relative risk with exposure level, which supports the temporal relationship.

If ETS causes lung cancer, then the true relative risk is small for detection by epidemiologic standards and may differ between countries as well. However, by considering the totality of the evidence, it is determined that the large accumulation of epidemiologic evidence from independent sources in different locales and circumstances, under actual exposure conditions, is adequate for conclusiveness. Having accounted for variable study size, adjusted for a possible systematic spousal bias due to smoker misclassification, and considered potential bias, confounding, and other sources of uncertainty on a study-by-study basis, *consistency* of a significant association is clearly evident for the summary statistical measures for Tiers 1 through 2 and 1 through 3 in Greece, Hong Kong, Japan, and the United States. The combined countries from Western Europe are similar in outcome to the United States, although significance is not attained. There is too much obscurity and uncertainty attached to the studies in China for adequate data interpretation.

The relative risks for each country are obtained by pooling estimates from the epidemiologic studies conducted in the country. The *strength of association* is limited by the true value of the relative risk, which is small. Statistical significance is attained, however, for the pooled studies of the United States and most other countries. The data were obtained from actual conditions of environmental exposure; therefore, imprecision is not increased by extrapolation of results from atypically high exposure concentrations, a common situation in risk analysis. Additionally, all studies were individually corrected for systematic bias from smoker misclassification at the outset, and qualitative characteristics of the studies were carefully reviewed to emphasize the results from the studies with higher utility for the objectives of this report. The outcome for the United States is heavily influenced by the large National Cancer Institute study (FONT) that was specifically designed and executed to avoid methodological problems that might undermine the accuracy or precision of the results.

Of the 14 studies reporting a test for upward trend, 10 are statistically significant at 0.05 (see Table 5-12) which would occur by chance alone with probability less than 10^{-9}. This evidence of *dose response* is very supportive of a causal interpretation because it would be an unlikely result of any operative sources of bias or confounding.

Specificity does not apply to ETS. Although ETS has been assessed for the same endpoint (lung cancer) in all studies, the occurrence of lung cancer is not specific to ETS exposure. Data on histological cell type are not conclusive. The study by Fontham and colleagues (1991) suggests that adenocarcinoma may be more strongly related to ETS exposure than other cell types. Adenocarcinoma, however, does not appear to be etiologically specific to ETS.

Biomarkers such as cotinine/creatinine levels clearly indicate that ETS is taken up by the lungs of nonsmokers (see Chapter 3). The similarity of carcinogens identified in sidestream and mainstream smoke, along with the established causal relationship between lung cancer and smoking in humans with high relative risks and dose-response relationships in four different lung cell types down to low exposure levels, provide *biological plausibility* that ETS is also a lung carcinogen (Chapter 4). In addition, animal models and genotoxicity assays provide corroborating evidence for the carcinogenic potential of ETS (Chapter 4). The epidemiologic data provide independent empirical verification of the anticipated risk of lung cancer from passive smoking and also an estimate of the increased risk of lung cancer to never-smoking women. The *coherence* of results from these three approaches and the lack of significant arguments to the contrary strongly support causality as an explanation of the observed association between ETS exposure and lung cancer.

5.6.3. Conclusion

Based on the assessment of all the evidence considered in Chapters 3, 4, and 5 of this report and in accordance with the EPA *Guidelines* and the causality criteria above for interpretation of human data, this report concludes that ETS is a Group A human carcinogen, the EPA classification "used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer" (U.S. EPA, 1986a).

6. POPULATION RISK OF LUNG CANCER FROM PASSIVE SMOKING

6.1. INTRODUCTION

The preceding chapter addressed the topic of hazard identification and concluded that environmental tobacco smoke (ETS) exposure is causally associated with lung cancer. If an effect is large enough to detect in epidemiologic studies investigating the consequences of ETS exposure at common exposure levels, the individual risk associated with exposure is considered to be high compared with most environmental contaminants assessed. Of course, the number of lung cancer deaths attributable to ETS exposure for a whole population, such as the United States, depends on the number of persons exposed as well as the individual risk. Studies of cotinine/creatinine concentrations in nonsmokers indicate that ETS is virtually ubiquitous. For example, in urinary bioassays of 663 nonsmokers, Cummings et al. (1990) found that over 90% had detectable levels of cotinine. Among the 161 subjects who reported no recent exposure to ETS, the prevalence of detectable cotinine was still about 80%. Although the average cotinine level for all those tested may be below the average for subjects exposed to spousal ETS, as studied in this report, it indicates uptake of ETS to some extent by a large majority of nonsmokers (see also Chapter 3). Consequently, exposure to ETS is a public health issue that needs to be considered from a national perspective.

This chapter derives U.S. lung cancer mortality estimates for female and male never-smokers and long-term (5+ years) former smokers. Section 6.2 discusses prior approaches to estimating U.S. population risk. Section 6.3 presents this report's estimates. First, the parameters and formulae used are defined (Section 6.3.2), and then lung cancer mortality estimates are calculated from two different data sets and confidence and sources of uncertainty in the estimates are discussed. Section 6.3.3 derives estimates based on the combined relative risk estimates of the 11 U.S. studies from Chapter 5. Section 6.3.4 bases its estimates on the data from the single largest U.S. study, that of Fontham et al. (1991). Finally, Section 6.3.5 discusses the sensitivity of the estimates to changes in various parameter values. ETS-attributable lung cancer mortality rates (LCMR) for each of the individual studies from Chapter 5 are presented in Appendix C.

6.2. PRIOR APPROACHES TO ESTIMATION OF POPULATION RISK

Several authors have estimated the population risk of lung cancer from exposure to ETS. Two approaches have been used almost exclusively. One approach analyzes the overall epidemiologic evidence available from case-control and cohort studies, as done in this report; the other estimates a dose-response relationship for ETS exposure extrapolated from active smoking, based on "cigarette-equivalents" determined from a surrogate measure of exposure common to passive and active smoking. A recent review of risk assessment methodologies in passive smoking may be found in Repace and Lowrey (1990).

6.2.1. Examples Using Epidemiologic Data

The National Research Council report (NRC, 1986) is a good example of the epidemiologic approach. An overall estimate of relative risk (RR) of lung cancer for never-smokers exposed to both spousal smoking and background ETS versus those exposed only to background ETS is obtained by statistical summary across all available studies. Two "corrections" are then made to the estimate of RR to correct for the two sources of systematic bias. The first correction accounts for expected upward bias from former smokers and current smokers who may be misclassified as never-smokers; this correction results in a decrease in the RR estimate. The second correction is an upward adjustment to the RR taking into account the risk from background exposure to ETS (experienced by a never-smoker whether married to a smoker or not) to obtain estimates of the excess lung cancer risk from all sources of ETS exposure (spousal smoking and background ETS) relative to the risk in an ETS-free environment. Population risk can then be characterized by estimating the annual number of lung cancer deaths among never-smokers attributable to all sources of ETS exposure. This calculation requires the final corrected estimates of RR (one for background ETS only and one for background plus spousal smoking), the annual number of lung cancer deaths (LCDs) from all causes in the population assessed (e.g., never-smokers of age 35 and over), and the proportion of that population exposed to spousal smoking. The entire population is assumed to be exposed to some average background level of ETS; although, in fact, the population contains some individuals with high exposure and others with virtually no exposure.

The NRC report combines data for female and male never-smokers to obtain an overall observed RR estimate of 1.34 (95% confidence interval [C.I.] = 1.18, 1.53), but this estimate is most heavily influenced by the abundant female data. (The female data alone generate a combined RR estimate of 1.32 [95% C.I. = 1.18, 1.52], while the male data produce an RR estimate of 1.62 [95% C.I. = 0.99, 2.64].) To adjust for potential misclassification bias, the NRC uses the construct of Wald and coworkers. The technical details of the adjustment are contained in Wald et al. (1986) and to a lesser degree in the NRC report. After correcting the overall observed RR estimate of 1.34 downward for an expected positive (upward) bias from smoker misclassification, the NRC concludes that the relative risk is about 1.25, and probably lies between 1.15 and 1.35. Correction for background sources (i.e., nonspousal sources of ETS) increases the NRC estimate of RR for an "exposed" person (i.e., exposed to ETS from spousal smoking) to 1.42 (range of 1.24 to 1.61); the change is due only to implicit redefinition of RR to mean risk relative to zero-ETS exposure instead of relative to nonspousal sources of ETS. Under this redefinition, the RR for an "unexposed" person (i.e., unexposed to spousal ETS) versus a truly unexposed person (i.e., in a zero-ETS environment) becomes 1.14 (range of 1.08 to 1.21). The NRC report further estimates that about 21% of the lung cancers in nonsmoking women and 20% in nonsmoking men may be attributable to exposure to ETS (NRC, 1986, Appendix C); these estimates, however, are based on RRs corrected for background ETS but not for smoker misclassification. Applying these percentages to estimates of 6,500 LCDs in never-smoking women and 3,000 LCDs in never-smoking men in 1988 (American Cancer Society, personal communication), the number attributable to ETS exposure is 1,365 and 600, respectively, for a total of about 2,000 LCDs among never-smokers of both sexes.

Robins (NRC, 1986, Appendix D [included in the NRC report but neither endorsed nor rejected by the committee]) explores three approaches to assessment of lung cancer risk from exposure to ETS, each with attendant assumptions clearly stated. A related article by Robins et al. (1989) contains most of the same information. Method 1 is based solely on evaluation of the epidemiologic data applying two assumptions: (1) correction of relative risk for background exposure to ETS independent of age, and (2) the excess relative risk in a nonsmoker is proportional to the lifetime dose of ETS. In this method, Robins uses a weighted average RR of 1.3. After correcting this RR for background ETS exposure, age-adjusted population-attributable risks are calculated for females and males separately. Adjusting Robins' results to 6,500 annual LCDs in female never-smokers and 3,000 LCDs in male never-smokers, for comparison purposes, yields estimates of 1,870 female LCDs and 470 male LCDs attributable to ETS. Method 2 uses an overall relative risk value based on epidemiologic data, but also makes some assumptions to appeal to results of Day and Brown (1980) and Brown and Chu (1987) on lung cancer risk in active smokers. Again, adjusting Robins' estimates to 6,500 female LCDs and 3,000 male LCDs, the range of excess LCDs attributable to ETS is 1,650 to 2,990 for never-smoking females and 420 to 1,120 for never-smoking males. Method 3 is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

The Centers for Disease Control (CDC) has published an estimate of 3,825 (2,495 female and 1,330 male) deaths in nonsmokers from lung cancer attributable to passive smoking for the year 1988 (CDC, 1991a), with reference to the NRC report of 1986. Those figures are the midrange of values for males and females from method 2 of Robins in Appendix D of the NRC report (NRC, 1986).

Blot and Fraumeni (1986) published a review and discussion of the available epidemiologic studies about the same time that the reports of the Surgeon General and NRC appeared. The set of studies considered by Blot and Fraumeni are almost identical to those included in the NRC report, except for omission of one cohort study (Gillis et al., 1984), and inclusion of Wu et al.

(1985), the case-control study excluded by the NRC because the raw data were unpublished. An overall relative risk estimate calculated from the raw data for females yields 1.3 (95% C.I. = 1.1, 1.5). When the results are combined for high-exposure categories, the overall relative risk estimate is 1.7 (1.4, 2.1).

Wells (1988) provides a quantitative risk assessment that includes several epidemiologic studies subsequent to the NRC and Surgeon General's reports of 1986 (NRC, 1986; U.S. DHHS, 1986). Like the NRC report, the epidemiologic data for both women and men are considered, for which Wells provides separate estimates of overall relative risk and attributable risk. Wells calculates an overall relative risk of 1.44 (95% C.I. = 1.26, 1.66) for females and 2.1 (1.3, 3.2) for males. Following the general approach of Wald et al. (1986), the misclassification percentage for ever-smokers is assumed to be 5% (compared to 7% for Wald et al.). Rates are corrected for background exposure to ETS, except in studies from Greece, Japan, and Hong Kong, where the older nonsmoking women are assumed to experience very little exposure to ETS outside the home. A refinement in the estimation of population-attributable risk is provided by adjusting for age at death (which also appears in the calculations of Robins, NRC, Appendix D). The calculation of population-attributable risk applies to former smokers as well as never-smokers, which is a departure from Wald et al. and the NRC report. The annual number of LCDs attributable to ETS in the United States is estimated to be 1,232 (females) and 2,499 (males) for a total of 3,731. About 3,000, however, is thought to be the best current estimate (Wells, 1988). (In addition to the estimates of ETS-attributable LCDs, Wells uses the epidemiological approach to derive estimates of ETS-attributable deaths from other cancers--11,000--and from heart disease--32,000.)

Saracci and Riboli (1989), of the International Agency for Research on Cancer (IARC), review the evidence from the 3 cohort studies and 11 of the case-control studies (Table 4-1). The authors follow the example of the NRC and Wald et al. with respect to the exclusion of studies, and add only one additional case-control study (Humble et al., 1987). The overall observed relative risk for the studies, 1.35 (95% C.I. = 1.20, 1.53), is about the same as that reported by the NRC, 1.34 (1.18, 1.53). It is not reported how the overall relative risk was calculated.

Repace and Lowrey (1985) suggest two methods to quantify lung cancer risk associated with ETS. One method is based on epidemiologic data, but, unlike the previous examples, Repace and Lowrey use a study comparing Seventh-Day Adventists (SDAs) (Phillips et al., 1980a,b) with a demographically and educationally matched group of non-SDAs who are also never-smokers to obtain estimates of the relative risk of lung cancer mortality, in what they describe as a "phenomenological" approach. The SDA/non-SDA comparison provides a basis for assessing lung cancer risk from ETS in a broader environment, particularly outside the home, than the other epidemiologic studies. It also serves as an independent source of data and an alternative approach for comparison. Information regarding the number of age-specific LCDs and person-years at risk for the two cohorts is obtained from the study. The basis for comparison of the two groups is the premise that the non-SDA cohort is more likely to be exposed to ETS than the SDA group due to differences in lifestyle. Relatively few SDAs smoke, so an SDA never-smoker is probably less likely to be exposed at home by a smoking spouse, in the workplace, or elsewhere, if associations are predominantly with other SDAs. One of the virtues of this novel approach is that it contributes to the variety of evidence for evaluation and provides a new perspective on the topic.

Phillips et al. (1980 a,b) reported that the non-SDA cohort experienced an average LCMR equal to 2.4 times that of the SDA cohort. Using 1974 U.S. Life Tables, Repace and Lowrey calculate the difference in LCMR for the two cohorts by 5-year age intervals and then apply this value to an estimated 62 million never-smokers in the United States in 1979 to obtain the number of LCDs attributable to ETS annually. The result, 4,665, corresponds to a risk rate of about 7.4 LCDs per 100,000 person-years. In an average lifespan of 75 years, that value equates to 5.5 deaths per 1,000 people exposed. The second method described by Repace and Lowrey is a "cigarette-equivalents" approach and is discussed in Section 6.2.2.

Wigle et al. (1987) apply the epidemiologic evidence from the SDA/non-SDA study (Phillips et al., 1980a,b) to obtain estimates of the number of LCDs in never-smokers due to ETS in the population of Canada. The estimated number of deaths from lung cancer attributable to passive smoking is calculated separately for males and females, using age-specific population figures for Canada and the age-specific rates of death from lung cancer attributable to ETS estimated by Repace and Lowrey (1985). A total of 50 to 60 LCDs per year is attributed to spousal smoking alone, with 90% of them in women. Overall, involuntary exposure to tobacco smoke at home, work, and elsewhere may cause about 330 LCDs annually.

6.2.2. Examples Based on Cigarette-Equivalents

The cigarette-equivalents approach assumes that the dose-response curve for lung cancer risk from active smoking also applies to passive smoking, after extrapolation of the curve to lower doses and conversion of ETS exposure into an "equivalent" exposure from active smoking, determined from a surrogate measure of exposure common to passive and active smoking. Relative cotinine concentrations in body fluids (urine, blood, or saliva) of smokers versus nonsmokers and tobacco smoke particulates in sidestream smoke (SS) and mainstream smoke (MS) have commonly been used for this purpose. The lung cancer risk of ETS is assumed to equal the risk from active smoking at the rate determined by the cigarette-equivalents. For example, suppose the average cotinine concentration in exposed never-smokers is 1% of the average value found in people who smoke 30 cigarettes per day. The lung cancer risk for a smoker of (0.01)30 =

0.3 cigarettes per day is estimated by low-dose extrapolation from a dose-response curve for active smoking, and that value is used to describe the lung cancer risk for ETS exposure. This general explanation describes the nature of the approach; however, authors vary in their constructed solutions and level of detail. The basic assumption of cigarette-equivalents procedures is that the lung cancer risks in passive and active smokers are equivalently indexed by the common measure of exposure to tobacco smoke, i.e., a common value of the surrogate measure of exposure in an active and a passive smoker would imply the same lung cancer risk in both. This assumption may not be tenable, however, as MS and SS differ in the relative composition of carcinogens and other components identified in tobacco smoke and in their physicochemical properties in general; the lung and systemic distribution of chemical agents common to MS and SS are affected by their relative distribution between the vapor and particle phases, which differs between MS and SS and changes with SS as it ages. Active and passive smoking also differ in characteristics of intake; for example, intermittent (possibly deep) puffing in contrast to normal (shallow) inhalation, which may affect deposition and systemic distribution of various tobacco smoke components as well (see Sections 3.2 and 3.3.2).

Several authors have taken issue with the validity of the cigarette-equivalents approach. For example, Hoffmann et al. (1989), in discussing the longer clearance times of cotinine from passive smokers than from active smokers, conclude that "the differences in the elimination time of cotinine from urine preclude a direct extrapolation of cigarette-equivalents to smoke uptake by involuntary smokers." A recent consensus report of an IARC panel of experts (Saracci, 1989) states, "Lacking knowledge of which substances are responsible for the well-established carcinogenic effect of MS, it is impossible to accurately gauge the degree of its similarity to ETS in respect to carcinogenic potential." The Surgeon General's report devotes a three-page section to the concept of cigarette-equivalents, quantitatively demonstrating how they can vary as a measure of exposure (U.S. DHHS, 1986). It concludes that "these limitations make extrapolation from atmospheric measures to cigarette-equivalents units of disease risk a complex and potentially meaningless process." (On a lesser note, it has generally been assumed that the dose-response relationship for active smokers is reasonably well characterized. Recent literature raises some questions on this issue [Moolgavkar et al., 1989; Gaffney and Altshuler, 1988; Freedman and Navidi, 1987a,b; Whittemore, 1988].)

Citing cigarette-equivalents calculated in other sources, Vutuc (1984) assumes a range of 0.1 to 1.0 cigarettes per day for ETS exposure. Relative risks for nonsmokers are calculated for 10-year age intervals (40 to 80) based on the reported relationships of dose, time, and lung cancer incidence in Doll and Peto (1978). Relative risks for smokers of 0.1 to 1.0 cigarettes per day give a range in relative risk from 1.03 to 1.36. The author concludes that "as it applies to passive smokers, this range of exposures may be neglected because it has no major effect on lung cancer incidence." Vutuc assumes that his figures apply to both males and females. If an exposure fraction of 75% is assumed for both males and females, the range of relative risks given correspond to a range for population-attributable risk. If the number of LCDs among never-smokers in the United States in 1988 is about 6,500 females and 3,000 males (personal communication from the American Cancer Society), then the number of LCDs in never-smokers attributable to ETS is estimated to range from 240 to 2,020 (140 to 1,380 for females alone). So Vutuc's figures are consistent with several hundred excess LCDs among never-smokers in the United States. These estimates are from our extension of Vutuc's analysis, however, and are not the claim of the author.

Repace and Lowrey (1985) describe a cigarette-equivalents approach as an alternative to their "phenomenological" approach discussed in Section 6.2.1. One objective is to provide an assessment of exposure to ETS from all sources that is more inclusive and quantitative than might be available from studies based on spousal smoking. They consider exposure to ETS both at home and in the workplace, using a probability-weighted average of exposure to respirable suspended particulates (RSP) in the two environments. Exposure values are derived from their basic equilibrium model relating ambient concentration of particulates to the number of burning cigarettes per unit volume of air space and to the air change rate. From 1982 statistics of lung cancer mortality rates among smokers and their own previous estimates of daily tar intake by smokers, the authors calculate a lung cancer risk for active smokers of 5.8×10^{-6} LCDs/year per mg tar/day per smoker of lung cancer age. The essential assumption linking lung cancer risk in passive and active smokers is that inhaled tobacco tar poses the same risk to either on a per unit basis. Extrapolation of risk from exposure levels for active smokers to values calculated for passive smokers is accomplished by assuming that dose-response follows the one-hit model for carcinogenesis. An estimated 555 LCDs per year in U.S. nonsmokers (never-smokers and former smokers) are attributed to ETS exposure (for 1980). The ratio of total LCDs in 1988 to 1980 is approximately 1.37 (Repace, 1989). With that population adjustment factor, the approximate number of LCDs attributable to ETS among nonsmokers is closer to 760 for 1988 (including former smokers).

Method 3 of Robins (NRC, 1986, Appendix D--again, included in the NRC report but not specifically endorsed by the committee) extrapolates from data on active smoking, along with several assumptions. Applying his results to 6,500 females and 3,000 males, the range of excess LCDs in never-smokers due to ETS is 550 to 2,940 for females and 153 to 1,090 for males.

Russell and coworkers (1986) use data on urinary nicotine concentrations in smokers and nonsmokers to estimate exposure and risk from passive smoking. The risk of premature death from passive smoking is presumed to be in the same ratio to premature death in active smokers as the ratio of concentrations of urinary nicotine in passive to active smokers (about 0.007). Calculations are made using vital statistics for Great Britain and then extrapolated to the United States. The latter estimate, 4,000+ deaths per year due to passive smoking, is for all causes of death, not just LCDs.

Arundel et al. (1987) attributes only five LCDs among female never-smokers to ETS exposure. The corresponding figure for males is seven (both figures are adjusted to 6,500 females and 3,000 males). The expected lung cancer risk for never-smokers is estimated by downward extrapolation of the lung cancer risk per mg of particulate ETS exposure for current smokers. The authors' premise is that the lung carcinogenicity of ETS is entirely attributable to the particulate phase of ETS, and the consequent risk in passive smoking is comparable to active smoking on a per mg basis of particulate ETS retained in the lung. If the vapor phase of ETS were also considered, the number of LCDs attributable to ETS would likely increase (e.g., see Wells, 1991).

6.3. THIS REPORT'S ESTIMATES OF LUNG CANCER MORTALITY ATTRIBUTABLE TO ETS IN THE UNITED STATES

6.3.1. Introduction and Background

This report uses the epidemiologic approach because of the abundance of human data from actual environmental exposures. Furthermore, the assumptions are fewer and more valid than for the cigarette-equivalents approach. The report generally follows the epidemiologic methodology used by the NRC (NRC, 1986) and others (Section 6.2.1), with three important differences. The first difference is that the NRC combined the data on females and males for its summary relative risk estimate. This report uses only the data on females because there are likely to be true sex-based differences in relative risk due to differences in exposure to background ETS and differences in background (i.e., non-tobacco-smoke-related) lung cancer risk. Furthermore, the vast majority of the data are for females. The second difference is that the NRC combined study estimates of relative risk across countries for its summary relative risk estimate; this report combines relative risk estimates only within countries, and then bases the U.S. population risk assessment on the U.S. estimate only. As discussed in Chapter 5, there are apparently true differences in the observed relative risk estimates from different countries, which might reflect lifestyle differences, differences in background lung cancer rates in females, exposure to other indoor air pollutants, and differences in exposure to background levels of ETS. Therefore, for the purposes of U.S. population risk assessment, it is appropriate to use the U.S. studies; in addition, far more studies are currently available so there is less need to combine across countries. The third difference is that the NRC corrected its overall estimate of relative risk downward for smoker misclassification bias. In this report, the individual study estimates are corrected for smoker misclassification bias at the outset, i.e., prior to any analysis, using the particular parameters appropriate for each separate study (Appendix B).

The basic NRC model is defined as

$$RR(d_E) = (1 + Z * \beta d_N)/(1 + \beta d_N)$$

where $RR(d_E)$ is the relative risk for the group of never-smokers identified as "exposed" to spousal ETS (plus background ETS) compared with the group identified as "unexposed" (but actually exposed to background ETS); Z is the ratio between the operative mean dose level in the exposed group, d_E, and the mean dose level in the unexposed group, d_N; and β is the amount of increased risk per unit dose. The equation is only defined for $Z > RR(d_E) > 1$ (see Section 8.3).

The method used here is based on several assumptions: (1) that body cotinine levels in never-smokers are linearly related to ETS exposure; (2) that current ETS exposure is representative of past exposures; and (3) that the excess risk of lung cancer in nonsmokers exposed to ETS is linearly related to the dose absorbed.

Estimates of $RR(d_E)$ for female never-smokers were derived in Chapter 5, where they were corrected for smoker misclassification bias; these are redefined in Section 6.3.2 as RR_2. The relative risk estimates are then adjusted to be applicable to different baseline exposure groups in order to calculate population risks for never-smoking women. In order to extend the analyses to female former smokers and male never- and former smokers, the relative risks are converted to excess or additive risks. The use of additive risks is more appropriate for these groups because of the different baseline lung cancer mortality rates by sex and smoking status (former vs. never).

More specifically, estimates of ETS-attributable population mortality are calculated from female lung cancer mortality rates, which are themselves derived from summary relative risk estimates either from the 11 U.S. studies combined (Section 6.3.3) or from the Fontham et al. (1991) study alone (Section 6.3.4), along with other parameter estimates from prominent sources (Section 6.3.2). The LCMRs in this instance are defined as the number of LCDs in 1985 per 100,000 of the population at risk. The LCMR in U.S. women under age 35 is minuscule, so only persons of age 35 and above are considered at risk. Although these LCMRs are expressed as a mortality rate per 100,000 of the population at risk, as derived they are applicable only to the entire population at risk and not to any fraction thereof that might, for example, have a different average exposure or age distribution.

The LCMR for the subpopulation and exposure scenario to which the epidemiologic studies apply most directly--never-smoking females exposed to spousal ETS--is estimated first. That estimate is then incremented to include exposure to nonspousal ETS for all never-smoking females. For the ETS-attributable population mortality estimates, these LCMRs are applied to never-smoking males and former smokers at risk, as well as to the females at risk for which the rates were specifically derived. The most reliable component of the total estimate constructed for the United States is the estimate for the female never-smokers exposed to spousal ETS. The other components require additional assumptions, which are described. As the number of assumptions increases, so does the uncertainty of the estimates. Thus, the total estimate of lung cancer risk to U.S. nonsmokers of both sexes is composed of component estimates of varying degrees of certainty.

One might argue that smokers are among those most heavily exposed to ETS, since they are in close proximity to sidestream smoke (the main component of ETS) from their own cigarettes and are also more likely than never-smokers to be exposed to ETS from other smokers. The purpose of this report, however, is to address respiratory health risks from ETS exposure in nonsmokers. In current smokers, the added risk from passive smoking is relatively insignificant compared to the self-inflicted risk from active smoking.

6.3.2. Parameters and Formulae for Attributable Risk

Several parameters and formulae are needed to calculate attributable risk. These are presented in Table 6-1, with the derivations explained below.

The size of the target population, in this case the number of women in the United States of age 35+ in 1985, is denoted by N, with $N = N_1 + N_2$, where N_1 = the number of ever-smokers and N_2 = the number of never-smokers. The total number of LCDs from all sources, T, is apportioned into components from four attributable sources: (1) non-tobacco-smoke-related causes, the background causes that would persist in an environment free of tobacco smoke; (2) background ETS, which refers to all ETS exposure other than that from spousal smoking; (3) spousal ETS; and (4) ever-smoking. The risk from non-tobacco-smoke-related causes (source 1) is a baseline risk (discussed below) assumed to apply equally to the entire target population (never-smokers and ever-smokers alike). The ever-smoking component of attributable risk (source 4) refers to the incremental risk above the baseline in ever-smokers (this report does not partition the incremental risk in ever-smokers further into components due to background ETS and spousal ETS, except for long-term [5+ years] former smokers). The background ETS component (source 2) is the incremental risk above the baseline in all never-smokers from exposure to nonspousal sources of

Table 6-1. Definition and estimates of relative risk of lung cancer for 11 U.S. studies combined for various exposure sources and baselines; population parameter definitions and estimates used to calculate U.S. population-attributable risk estimates for ETS

DENOMINATOR (Baseline)	NUMERATOR of relative risk			
	All persons	Never-smokers ETS exposure		Current and former smokers
Source of exposure	Non-tobacco-smoke sources of exposure [nt]	Background ETS [nt]+[ETS$_B$]	Background ETS and spousal ETS [nt]+[ETS$_B$]+[ETS$_S$]	Active smoking [nt]+[ETS]+[ACT]
[nt]	1	RR$_{03}$ = 1.34	RR$_{02}$ = 1.59[1]	RR$_{01}$ = 13.8
[nt]+[ETS$_B$]	-	-	RR$_2$ = 1.19[2]	RR$_{11}$ = 10.3
[nt]+[ETS$_B$]+[ETS$_S$]	-	-	-	RR$_1$ = 9.26[3]

[1] Basic adjustment for background exposure with Z = 1.75.
[2] Pooled value from 11 U.S. studies for never-smoking females.
[3] RR$_1$ = a weighted average of 11.94 for women active smokers (63.4%) and 4.69 for women former smokers (36.6%) = 9.26.

Definitions and Estimates of Population Parameter Values

N = Total number of women in U.S. (1985) age 35+ = N$_1$ (ever-smokers) + N$_2$ (never-smokers) = 25.7 million + 32.3 million = 58 million.
P$_1$ = Prevalence (proportion) of female ever smokers age 35+ = 0.443.
P$_2$ = Proportion of NS women exposed to equivalent spousal ETS (plus background ETS) = 0.6.
Z = Ratio of body cotinine levels in (nonsmokers exposed to background ETS plus spousal ETS) to (nonsmokers exposed to background ETS only) = 1.75.
T = Total LCDs in United States in 1985 among women aged 35+ = 38,000.

ETS. The spousal ETS component (source 3) is the additional incremental risk in never-smokers exposed to spousal smoking.

The calculational formulae also require values for the parameters P_1 (prevalence of ever-smokers), P_2 (proportion of never-smokers exposed to spousal smoking), RR_1 (average lung cancer risk for ever-smokers relative to the average risk for never-smokers in the population), and RR_2 (lung cancer risk of never-smokers exposed to spousal ETS relative to never-smokers not exposed to spousal ETS). Additional parameters (RR_{11}, Z, RR_{01}, RR_{02}, and RR_{03}) are introduced or developed below.

The "baseline" risk is defined as the term in the denominator of a risk ratio. For example, in RR_1 the baseline risk is the lung cancer risk in a population of never-smokers with P_2 exposed to spousal ETS and $1 - P_2$ not exposed to spousal ETS. The conversion of RR_1 to the same baseline risk as RR_2 (the risk of never-smokers not exposed to spousal ETS but still exposed to non-tobacco-smoke-related causes and to background ETS), is given by

$$RR_{11} = RR_1(P_2RR_2 + 1 - P_2). \qquad (6\text{-}1)$$

To convert relative risks to the baseline risk of lung cancer from non-tobacco-smoke-related causes only (i.e., excluding background ETS in the baseline) requires some assumptions. Let RR_{02} denote the conversion of RR_2 to this new baseline. It is assumed that: (1) the excess risk of lung cancer from ETS exposure is proportional to ETS exposure; and (2) the ratio of ETS exposure from spousal smoking plus other sources to exposure from other sources alone, denoted by Z, is known and $Z > RR_2 > 1$. (For the values used in this report, this relation is true. See also the discussion in Section 8.3.) Under these assumptions, $RR_{02} = 1 + \beta Zd_N$ (from Section 6.3.1), or

$$RR_{02} = (Z - 1)/(Z/RR_2 - 1). \qquad (6\text{-}2)$$

Determination of a value for Z from data on cotinine concentrations (or cotinine/creatinine) is discussed below. The conversion of RR_1 to the same zero-ETS baseline risk as RR_{02} follows from multiplying expression (6-1) by RR_{02}/RR_2, i.e.,

$$RR_{01} = RR_1(P_2RR_{02} + (1 - P_2)RR_{02}/RR_2). \qquad (6\text{-}3)$$

The terms RR_{01} and RR_{02} are the lung cancer risks for ever-smokers and for never-smokers exposed to spousal ETS, respectively, relative to the risk for never-smokers in a zero-ETS environment. The risk of never-smokers not exposed to spousal ETS (but exposed to background ETS and nonsmoking causes) relative to the zero-ETS baseline risk is

$$RR_{03} = RR_{02}/RR_2. \tag{6-4}$$

The population-attributable risk of lung cancer in the total population for a source (risk factor) is a ratio. The numerators of the ratios for sources of tobacco smoke are:

current/former active smoking in ever-smokers,
$P_1(RR_{01} - 1)$; (6-5)

background ETS plus spousal ETS in never-smokers exposed to both,
$(1 - P_1)P_2(RR_{02} - 1)$; and (6-6)

background ETS in never-smokers not exposed to spousal ETS,
$(1 - P_1)(1 - P_2)(RR_{02}/RR_2 - 1)$. (6-7)

The denominator for each term is their sum plus one, i.e.,

$$Ex(6\text{-}5) + Ex(6\text{-}6) + Ex(6\text{-}7) + 1 \tag{6-8}$$

where Ex(6-5) refers to expression (6-5), etc. The population-attributable risk for remaining causes of lung cancer (non-tobacco-smoke-related background causes) is

$$1/Ex(6\text{-}8). \tag{6-9}$$

Multiplying the population-attributable risk for a source by the total number of LCDs yields the number of LCDs attributable to that source. An alternative and equivalent derivation of the source-attributable LCD estimates can be performed by first calculating LCMRs. LCMRs are obtained for each source as follows:

non-tobacco-smoke-related causes: $LCMR_{nt} = 10^5 Ex(6\text{-}9)T/N$.
ever-smoking: $LCMR_{nt}(RR_{01} - 1)$.
spousal ETS: $LCMR_{nt}(RR_{02} - RR_{03})$.
background ETS: $LCMR_{nt}(RR_{03} - 1)$.

Then the number of LCDs attributable to a source is estimated by multiplying the LCMR for that source by the total population at risk from that source.

We now consider parameter values for N, T, P_1, P_2, RR_1, and Z to be used with the value 1.19 for RR_2, the pooled estimate of RR_2 from the 11 U.S. studies (Table 5-17), for the population risk assessment in Section 6.3.3. The value used for RR_2 is then changed to 1.28, the estimate from the Fontham et al. (1991) study in the United States, and a new value of Z is constructed from the cotinine data in that study for the alternative population risk assessment calculations in Section 6.3.4. The female population in 1985 of age 18+ years of age is approximately 92 million (U.S. DHHS, 1989, Chapter 3). Detailed census data by age for 1988 indicate that the proportion of women 35+ years of age in the female population of age 18+ is 0.63 (U.S. Bureau of the Census, 1990). Applying that proportion to the 1985 population gives approximately 58 million women of aged 35+ in 1985, the value used for N. There were approximately 38,000 female LCDs in the United States in 1985 (U.S. DHHS, 1989), which is used as the value for T.

Using figures from the Bureau of the Census and the 1979/80 National Health Interview Survey, Arundel et al. (1987) estimate the number of women of age 35+ by smoking status, obtaining a value of 0.443 as the fraction of ever-smokers. The National Center for Health Statistics (as reported in U.S. DHHS, 1989) provides the proportion of the female population by smoking status (never, former, current) for 1987. When applied to figures from the Bureau of the Census (1990) for the female population by age group available for 1988, the same fractional value (0.443) is obtained. These sources suggest that the proportion of ever-smokers in the female population has been fairly constant between 1980 and 1987, so P_1 will be given the value 0.443. Multiplying N by P_1 gives an estimate of $N_1 = 25.7$ million ever-smokers, leaving $N_2 = 32.3$ million never-smokers.

RR_1 applies to ever-smokers, which consist of current and former smokers. The relative risks of current and former female smokers of age 35+ for the period 1982-1986 are estimated at 11.94 and 4.69, respectively, from data in the American Cancer Society's Cancer Prevention Study II (CPS-II; as reported in U.S. DHHS, 1989). For 1985, the composition of ever-smokers is 63.4% current smokers and 36.6% former smokers (CDC, 1989a). Using those percentages to weight the relative risks for ever-smokers and former smokers gives 9.26, which will be used as the value of RR_1.

The proportion of never-smokers exposed to spousal ETS in epidemiologic studies typically refers to married persons, so we need to consider how to treat unmarried persons as well in order to set a value for P_2. The American Cancer Society's CPS-II (reported in Stellman and Garfinkel, 1986) percentages for marital status of all women surveyed (not just never-smokers) are: married, 75.3; divorced, 5.1; widowed, 14.6; separated, 0.8; and single, 4.2. Our estimates of risk apply to married female never-smokers, which comprise about 75% of female never-smokers, so it is necessary to consider exposure to ETS in the remaining 25% of unmarried female never-smokers.

Cummings (1990) obtained urinary cotinine levels on a total of 663 self-reported never-smokers and former smokers. The cotinine levels were slightly higher in males than in females (9.6 and 8.2 ng/mL, respectively), and slightly more than one-half of the subjects were females. The average cotinine level was 10.7 ng/mL for married subjects if the spouse smoked and 7.6 ng/mL otherwise. The average cotinine levels reported by marital status are: married, 8.3 ng/mL; never married, 10.3 ng/mL; separated, 11.8 ng/mL; widowed, 10.4 ng/mL; and divorced, 9.2 ng/mL. The study, in which 7% of the subjects were of age 18 to 29, and 47% were of age 60 to 84, does not claim to be representative. Nevertheless, the results suggest that in terms of ETS exposure, an unmarried never-smoker is probably closer, on average, to a never-smoker married to a smoker (an exposed person) than to a never-smoker married to a nonsmoker (an unexposed person). This observation is also consistent with the findings of Friedman et al. (1983).

The proportion of never-smoking controls exposed to spousal smoking varies among studies in the United States. If we exclude studies of uncertain representativeness, the median value for the remaining studies is 0.6. From the evidence on ETS exposure to unmarried female never-smokers, it is reasonable to assume that their exposure to ETS, on average, is at least as large as the average background level plus 60% of the average exposure from spousal smoking. For the calculations needed from these figures, this assumption is equivalent to treating unmarried and married female never-smokers alike in terms of exposure to ETS (i.e., 60% exposed at a level equivalent to spousal smoking plus background and 40% exposed at the background level only). Consequently, the value $P_2 = 0.6$ is assumed to apply equally to married and unmarried female never-smokers.

The NRC report of 1986 uses $Z = 3$ for the ratio of ETS exposure from spousal smoking plus other sources to ETS exposure from nonspousal sources alone. That value was primarily based on data from Wald and Ritchie (1984), for men in Great Britain, although Lee (1987b) had reported a value of 3.3 for women in Great Britain. The results of Coultas et al. (1987) also were considered, wherein a value of 2.35 was observed for saliva cotinine levels in a population-based survey of Hispanic subjects in New Mexico. More recent data suggest that a lower value of Z may be more accurate for the United States. The study of 663 volunteers in Buffalo, New York, reported by Cummings et al. (1990), observed a value of 1.55 based on mean urinary cotinine levels among married females ($n = 225$; Cummings, 1990). A study by Wall et al. (1988) containing 48 nonsmokers observed a ratio of mean cotinine levels of 1.53. A survey of municipal workers at a health fair found a cotinine ratio of 2.48 for the 112 women surveyed, but the comparison is between women who shared living quarters with a smoker and those who did not

(Haley et al., 1989). The 10-country collaborative cotinine study conducted by IARC (Riboli et al., 1990) collected urinary cotinine samples from nonsmoking women in four groups totaling about 100 each--married to a smoker (yes, no) and employed (yes, no)--including two locations, Los Angeles and New Orleans, in the continental United States. The ratios of average cotinine/creatinine concentrations for women married to a smoker to women not married to a smoker range from 1.75 to 1.89 in New Orleans, when the percentage of women employed is assumed to be between 25% and 75%. The data from Los Angeles contain an abnormally high mean for women who are employed and also married to a smoker (a mean of 14.6 based on only 13 observations, compared to the other three means for Los Angeles of 2.1, 4.5, and 6.6), so only the two means for unemployed women (married to a smoker and married to a nonsmoker) were used. The resultant ratio of cotinine/creatinine concentrations is 1.45. Data from the Fontham et al. (1991) study of lung cancer and ETS exposure in five U.S. cities yield a Z of 2.0 based on mean urinary cotinine levels in 239 never-smoking women (data provided by Dr. Elizabeth Fontham).

Cotinine data exhibit variability both within and between subjects, as well as between studies due to different experimental designs, protocols, and geographical locations (see also Chapter 3). Most of the Z values from recent U.S. studies range between 1.55 and 2.0. A value of 1.75 for Z appears reasonable based on the available U.S. data and will be used in Section 6.3.3 along with the combined RR estimate from 11 U.S. studies (Chapter 5) to calculate ETS-attributable lung cancer mortality estimates. Z = 2.0 and Z = 2.6, which are based on *median* cotinine levels, will be used in Section 6.3.4 for alternative calculations of lung cancer mortality based on the results of the Fontham et al. (1991) study. The sensitivity of the lung cancer mortality estimates to changes in Z and other parameters is discussed in Section 6.3.5.

6.3.3. U.S. Lung Cancer Mortality Estimates Based on Results of Combined Estimates from 11 U.S. Studies

This section calculates ETS-attributable U.S. lung cancer mortality estimates based on the combined relative risk estimate (RR_2 = 1.19) derived in Chapter 5 for the 11 U.S. studies. Alternatively, the estimate from just the combined Tier 1 and Tier 2 studies (RR_2 = 1.22 from 8 of the 11; see Table 5-17) could have been used because these eight studies were assessed as having the greater utility in terms of evaluating the lung cancer risks from ETS; however, the results would be virtually the same because the relative risk estimates are so similar. It was therefore decided to use the data from all the U.S. studies for the purposes of the population risk assessment.

6.3.3.1. *U.S. Lung Cancer Mortality Estimates for Female Never-Smokers*

The parameter values presented in Section 6.3.2 are assumed along with $RR_2 = 1.19$. For $Z = 1.75$, $RR_{02} = 1.59$ (from expression 6-2, denoted hereafter as Ex(6-2); see also Table 6-1). Given those parameter values, the formulae in Section 6.3.2 yield the estimated lung cancer mortality for U.S. women in 1985 by smoking status (ever-smoker, never-smoker exposed to spousal ETS, and never-smoker not exposed to spousal ETS) and source (non-tobacco-smoke-related causes, background ETS in never-smokers, spousal ETS in never-smokers, and ever-smoking), as displayed in Table 6-2. The LCMR from non-tobacco-smoke-related causes ($LCMR_{nt}$) is estimated to be 9.4 per 100,000 and is assumed to apply equally to all persons in the target population, regardless of smoking status. The excess LCMR in never-smokers from exposure to background ETS is 3.2, with an additional 2.4 if exposed to spousal ETS. The excess LCMR in ever-smokers, which includes whatever effect exposure to ETS has on ever-smokers as well as the effect from active smoking, is 120.8.

In rounded figures, 5,470 (14.4%) of the 38,000 LCDs in U.S. women age 35 and over in 1985 are unrelated to smoking (active or passive). The remaining 32,530 LCDs (85.6% of the total) are attributable to tobacco smoke: 31,030 in 25.7 million ever-smokers and 1,500 in 32.3 million never-smokers. These 1,500 ETS-attributable LCDs in never-smokers account for about one-third of all LCDs in female never-smokers. Of the 1,500 LCDs, about 1,030 (69%) are due to background ETS, and 470 (31%) are from spousal ETS. In summary, the total 38,000 LCDs from all causes is due to non-tobacco-smoke-related causes, 5,470 (14.4%), occurring in ever-smokers and never-smokers; ever-smoking, i.e., the effects of past and current active smoking as well as ETS exposure, 31,030 (81.7%), occurring in ever-smokers; and background ETS, 1,030 (2.7%), and spousal ETS, 470 (1.2%), occurring in never-smokers. In other words, ever-smoking causes about 81.7% of the lung cancers in women age 35 and over; exposure to ETS from all sources accounts for some 3.9%; and causes unrelated to tobacco smoke are responsible for the remaining 14.4%. The LCDs in never-smokers attributable to ETS equal about 5% (1,500/31,030) of the total attributable to ever-smoking. Part of the mortality attributed to ever-smoking here, however, is due to ETS exposure in former smokers, to be taken into account in Section 6.3.3.3.

6.3.3.2. *U.S. Lung Cancer Mortality Estimates for Male Never-Smokers*

There are 11 studies worldwide of exposure to ETS and lung cancer in males. The studies and their respective relative risks are AKIB, 1.8; BROW, 2.2; BUFF, 33+ years' exposure, 1.6; CORR, 2.0; HUMB, 4.2; KABA, 1.0; LEE, 1.3; HIRA(Coh), 2.25; HOLE(Coh), 3.5; plus the data in Kabat (1990), 1.2; and Varela (1987, Table 13 scaled down to 50 years of exposure), 1.2. (Data

Table 6-2. Estimated female lung cancer mortality by attributable sources for United States, 1985, using the pooled relative risk estimate from 11 U.S. studies[1]

			Lung cancer mortality[2]				
		(1)	(2)	(3)	(4)	(5)	
Smoking status[3]	Exposed to spousal ETS	Number at risk (in millions)	Non-tobacco-smoke-related causes[4]	Background ETS	Spousal ETS	Ever-smoking	Total
NS	No	12.92	1,220 (3.2)	410 (1.1)			
NS	Yes	19.38	1,830 (4.8)	620 (1.6)	470 (1.2)		
ES		25.69	2,420 (6.4)			31,030[5] (81.7)	
Total		58.00	5,470 (14.4)	1,030 (2.7)	470 (1.2)	31,030 (81.7)	38,000

[1] Percentage of grand total (38,000) in parentheses.

[2] The nonblank entries in the table are the product of an individual's attributable risk of lung cancer from non-tobacco-smoke-related causes (expression 6-9 (38,000/58,000,000)), the number at risk in column (1), and the following column-specific multiples:
Col. (2) 1
Col. (3) $RR_{03} - 1$
Col. (4) $RR_{02} - RR_{03}$
Col. (5) $RR_{01} - 1$

[3] NS = never-smokers; ES = ever-smokers.

[4] Background sources in the absence of tobacco smoke (i.e., in a zero-ETS environment).

[5] This figure attributes all lung cancer in ever-smokers above the background non-tobacco-smoke-related rate to ever-smoking.

for BROW, BUFF, and HUMB were supplied via personal communication from Drs. Brownson, Buffler, and Humble.) A weighted average of the passive smoking risk (RR_2) from these 11 studies is about 1.6. For the seven U.S. studies, BROW, BUFF, CORR, HUMB, KABA, Kabat (1990), and Varela (1987), the weighted average RR is about 1.4, but this value is heavily weighted (about 66%) by the Kabat (1990) and Varela (1987) studies, neither of which was used in the analysis of the female data. The combined risk for the five U.S. studies not including Kabat (1990) and Varela (1987) is about 1.8, but they are all small, low-weight studies. In any case, the observed relative risks for males appear to be at least as great as those for females.

When an attempt is made to correct the observed male risks for smoker misclassification, however, using the procedures outlined in Appendix B and the community survey-based misclassification factors for males (1.6% for current regular smokers, 15% for current occasional smokers, and 5.9% for former smokers), it is found that for most of these cohorts, the number of smokers misclassified as never-smokers either exceeds the relatively small number of observed never-smokers or is so great as to drive the corrected relative risk substantially below unity. This implies that the misclassification factors from the community surveys are too high to accurately correct the risks in the epidemiologic studies. Until better misclassification data on males are available, no real sense can be made of the male passive smoking relative risks.

Given the greater stability of the more extensive database on females, it was decided to apply the incremental LCMRs for spousal and nonspousal ETS exposure in female never-smokers to male never-smokers. The incremental LCMRs were used instead of the relative risk estimates because relative risk depends on the background risk of lung cancer (from non-tobacco-related causes) as well as the risk from ETS, and background lung cancer risk may differ between females and males. From Section 6.3.3.1, the LCMR from spousal ETS exposure was 2.4 per 100,000 at risk, and the LCMR from nonspousal ETS exposure was 3.2 per 100,000. The 1985 male population age 35 and over is 48 million (U.S. DHHS, 1989), of whom 27.2% (private communication from Dr. Ronald W. Wilson of the U.S. National Center for Health Statistics), or 13.06 million, were never-smokers. Of these, 24% (Wells, 1988), or 3.13 million, were spousally exposed. Applying the female ETS LCMRs, 3.13 million × 2.4/100,000 = 80 deaths in males from spousal ETS exposure and 13.06 million × 3.2/100,000 = 420 deaths from nonspousal exposure, for a total of 500 ETS-attributable LCDs among never-smoking males. These estimates based on female LCMRs are believed to be conservatively low because males generally have higher exposure to background ETS than females. This would lead to lower Z values and subsequently higher estimates of deaths attributable to background (nonspousal) ETS sources. In conclusion, confidence in these estimates for male never-smokers is not as high as those for female never-smokers.

6.3.3.3. *U.S. Lung Cancer Mortality Estimates for Long-Term (5+ Years) Former Smokers*

Because the risk of lung cancer from active smoking decreases with the number of years since smoking cessation (Section 4.2.2), passive smoking may be a significant source of lung cancer risk in long-term former smokers. There is, however, a scarcity of data on the relative risks of lung cancer for former smokers exposed to ETS. With former smokers, it is unknown how much of the observed lung cancer mortality is attributable to non-tobacco-smoke-related causes, how much is due to ETS exposure, and how much is accounted for by prior smoking. Consequently, neither the observational data on the number of lung cancers in the former smokers nor the relative risk data from never-smoking females are utilized. Instead, long-term former smokers are assumed to have the same LCMR from exposure to ETS as never-smoking females, as was assumed above for never-smoking males. In this manner, the lung cancer risk from ETS exposure can be calculated as an additional risk, supplemental to any remaining risk from previous active smoking. There is some uncertainty in the application of this assumption because the additional risk to long-term former smokers from ETS exposure may not, in fact, be the same as the risk to never-smokers. For example, ETS may have a greater promotional effect on former smokers because of their previous exposures to high concentrations of carcinogens from active smoking.

Female ever-smokers comprise about 44.3%, or 25.7 million, of the total U.S. female population age 35 and over of 58 million. Long-term (5+ years) former smokers comprise about 34% of these ever-smokers (U.S. DHHS, 1990b), or about 8.7 million women. Using a 2.2 concordance factor for former smokers married to ever-smokers versus never-smokers married to never-smokers (see Appendix B), it is estimated that about 77% of the former smokers, or about 6.7 million, would be spousally exposed compared with the 60% for the never-smokers. Thus, based on the LCMRs derived for female never-smokers, the expected number of ETS-attributable LCDs for female long-term former smokers would be 6.7 million × 2.40/100,000 = 160 deaths from spousal exposure and 8.7 million × 3.20/100,000 = 280 deaths from nonspousal exposure, for a total of 440.

Male ever-smokers comprise 72.8% of the U.S. male population, age 35 and over, of 48 million, equal to 35 million; of these, about 43% (derived from data in U.S. DHHS, 1990b, page 60, Table 5), or about 15 million, are 5+ year quitters. Of the never-smoking males, 24% were married to smokers (Section 6.3.3.2). Again using a 2.2 concordance factor for former smokers, it is estimated that 41% of the 15 million former smoking males, or 6.2 million, would be married to ever-smokers. Applying the female never-smoker LCMRs from Section 6.3.3.1, 6.2 million × 2.40/100,000 = 150 deaths from spousal ETS exposure and 15 million × 3.20/100,000 = 480 deaths from nonspousal ETS exposure for a total of 630 ETS-attributable LCDs among male long-term former smokers.

Table 6-3 displays the resultant estimates for LCDs attributable to background ETS and spousal ETS by sex for never-smokers and for former smokers who have quit for at least 5 years. The LCMRs for background ETS and spousal ETS, assumed to be independent of smoking status and sex, are the same as derived in Section 6.3.3.1 for female never-smokers (3.2 and 2.4, respectively). Background ETS accounts for about 2,200 (72%) and spousal ETS for 860 (28%) of the total due to ETS. Of the 3,060 ETS-attributable LCDs, about two-thirds are in females (1,930, 63%) and one-third in males (1,130, 37%). More females are estimated to be affected because there are more female than male never-smokers. By smoking status, two-thirds are in never-smokers (2,000, 65%) and one-third in former smokers who have quit for at least 5 years (1,060, 35%).

The numbers shown in Table 6-3 depend, of course, on the parameter values assumed for the calculations. The sensitivity of the totals in Table 6-3 to alternative parameter values is addressed in Section 6.3.5. First, however, tables equivalent to Tables 6-2 and 6-3 are developed based on the FONT study alone for comparison.

6.3.4. U.S. Lung Cancer Mortality Estimates Based on Results of the Fontham et al. (1991) Study (FONT)

The estimate of RR_2 (1.19), the risk of lung cancer to female never-smokers with spousal ETS exposure relative to the risk for female never-smokers without spousal ETS exposure, used in Section 6.3.3, is based on the combined outcomes of the 11 U.S. epidemiologic studies from Chapter 5 (see Table 5-17). In this section, the quantitative population impact assessment is repeated with FONT, the single U.S. study with Tier 1 classification (Section 5.4.4), as the source of the estimates of RR_2 and Z (constructed from urine cotinine measures), with the remaining parameter values left unchanged. While a single study has lower power and larger confidence intervals on the relative risk estimate than can be obtained by combining the various U.S. studies, using the specific data from a single study decreases the uncertainties inherent in combining results from studies that are not fully comparable. **FONT is the only study of passive smoking and lung cancer that collected cotinine measurements, thus providing estimates for RR_2 and Z from a single study population.** The total number of lung cancers attributable to total ETS exposure is particularly sensitive to those two parameters (discussed in Section 6.3.5).

The NCI-funded Fontham et al. study (1991) is a large, well-conducted study designed specifically to investigate lung cancer risks from ETS exposure (see also the critical review in

Table 6-3. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using 11 U.S. studies (never-smokers and former smokers who have quit 5+ years)[1]

				Lung cancer mortality			
Smoking status[2]	Sex	Exposed to spousal ETS	(1) Number at risk (in millions)	(2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	410		410	1,500 (NS,F)
NS	F	Yes	19.38	620	470	1,090	
NS	M	No	9.93	320		320	500 (NS,M)
NS	M	Yes	3.13	100	80	180	
FS	F	No	2.0	60		60	430 (FS,F)
FS	F	Yes	6.7	210	160	370	
FS	M	No	8.8	280		280	630 (FS,M)
FS	M	Yes	6.2	200	150	350	
Total			69.07	2,200 (71.9)	860 (28.1)	3,060	3,060

[1] Percentage of total ETS-attributable lung cancer deaths (3,060) in parentheses.
[2] NS = never-smokers; FS = former smokers who have quit 5+ years ago.

Appendix A). It addresses some of the methodological issues that have been of concern in the interpretation of results regarding lung cancer and passive smoking: smoker misclassification, use of surrogate respondents, potential recall bias, histopathology of the lung tumors, and possible confounding by other factors (see also Sections 5.3, 5.4.2, and 5.4.3). Cases and controls were drawn from five major cities across the United States (Atlanta, New Orleans, Houston, Los Angeles, and San Francisco) and, hence, should be fairly representative of the general U.S. population, at least of urban areas with moderate climates. Furthermore, the results of the study are consistent across the five cities.

In spite of the care incorporated into the FONT design to avoid smoker misclassification bias, some might still exist; thus, the adjusted relative risk of 1.29 reported in FONT is "corrected" slightly to 1.28 in this report. The parameter P_2, the proportion of never-smokers exposed to spousal ETS, was assigned the value 0.60 in the preceding section. In FONT, the observed proportion of spousal-exposed controls is 0.60 (0.66) for spousal use of cigarettes only (any type of tobacco) among colon-cancer controls and 0.56 (0.63) in population controls. Consequently, the previous value of 0.60 is retained. Of the 669 FONT population controls, whose current cotinine levels are considered the most representative of typical ETS exposure, there were 59 living with a current smoker and 239 whose spouses never smoked. (The other 371 were nonsmoking women who either no longer lived with a smoking spouse or whose spouse was a former smoker.) The *mean* cotinine level for never-smoking women with spouses who are current smokers ($n = 59$) is 15.90 ± 16.46; the mean level for the other 239 was 7.97 ($\pm$ 11.03). The ratio is 15.90/7.97, giving $Z = 2.0$ (data provided by Dr. Elizabeth Fontham). The median is a measure of central tendency that is less sensitive to extremes, so the ratio of *median* cotinine levels is also considered ($Z = 11.4/4.4 = 2.6$). Results for both values of Z are displayed in Tables 6-4 and 6-5, which correspond to Tables 6-2 and 6-3, respectively, of the previous sections for direct comparison.

The results of Section 6.3.2 are based on $RR_2 = 1.19$ (combined U.S. study results) and $Z = 1.75$ (from studies on cotinine levels). In this section, RR_2 and Z are both increased (RR_2 to 1.28 and Z to 2.0 and 2.6). Correcting $RR_2 = 1.28$ for background ETS exposure yields estimates of $RR_{02} = 1.78$ (i.e., the relative risk from spousal and background ETS) for $Z = 2.0$, and $RR_{02} = 1.55$ for $Z = 2.6$. The relative risk estimate from exposure to background ETS only becomes $RR_{03} = 1.39$ for $Z = 2.0$, and $RR_{03} = 1.21$ for $Z = 2.6$. The change in RR_2, from 1.19 to 1.28, increases the estimated number of LCDs from background and spousal ETS, whereas increasing Z decreases the figure for background ETS and has no effect on the number for spousal ETS (see Tables 6-2 and 6-4). Relative to the total ETS-attributable LCD estimate in the last section

Table 6-4. Female lung cancer mortality estimates by attributable sources for United States, 1985, using both the relative risk estimates and Z values from the Fontham et al. (1991) study[1]

			Lung cancer mortality[2]				
Smoking status[3]	Exposed to spousal ETS	(1) Number at risk (in millions)	(2) Non-tobacco-smoke-related causes[4]	(3) Background ETS	(4) Spousal ETS	(5) Ever-smoking	Total
NS	No	12.92	1,120 (2.9) *1,280 (3.4)*	440 (1.2) *270 (0.7)*			
NS	Yes	19.38	1,680 (4.4) *1,920 (5.1)*	660 (1.7) *410 (1.1)*	660 (1.7) *660 (1.7)*		
ES		25.69	2,230 (5.9) *2,550 (6.7)*			31,220[5] (82.2) *30,900[5] (81.3)*	
Total		58.00	5,030 (13.2) *5,760 (15.2)*	1,100 (2.9) *680 (1.8)*	660 (1.7) *660 (1.7)*	31,220 (82.2) *30,900 (81.3)*	38,000

[1] Percentage of grand total (38,000) in parentheses. Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.
[2] See Table 6-2 for formulae for table entries.
[3] NS = never-smokers; ES = ever-smokers.
[4] Baseline lung cancer mortality in the absence of tobacco smoke (i.e., in a zero-ETS environment).
[5] This figure attributes all lung cancer in ever-smokers above the non-tobacco-smoke-related rate to active smoking.

Table 6-5. Female and male lung cancer mortality estimates by attributable ETS sources for United States, 1985, using the Fontham et al. (1991) study (never-smokers and former smokers who have quit 5+ years)[1,2]

				Lung cancer mortality			
Smoking status[3]	Sex	Exposed to spousal ETS	(1) Number at risk (in millions)	(2) Background ETS	(3) Spousal ETS	(4) Total ETS	Total ETS by sex and smoking status
NS	F	No	12.92	440 *270*		440 *270*	1,760 *1,340* (NS,F)
NS	F	Yes	19.38	660 *410*	660 *660*	1,320 *1,070*	
NS	M	No	9.93	340 *210*		340 *210*	560 *390* (NS,M)
NS	M	Yes	3.13	110 *70*	110 *110*	220 *180*	
FS	F	No	2.0	70 *40*		70 *40*	530 *410* (FS,F)
FS	F	Yes	6.7	230 *140*	230 *230*	460 *370*	
FS	M	No	8.8	300 *190*		300 *190*	720 *530* (FS,M)
FS	M	Yes	6.2	210 *130*	210 *210*	420 *340*	
Total			69.07	2,360 (66.1) *1,460 (54.7)*	1,210 (33.9) *1,210 (45.3)*	3,570 *2,670*	3,570 *2,670*

[1] Calculations using Z = 2.0 (ratio of mean cotinine levels) are shown in regular typeface. Outcomes using Z = 2.6 (ratio of median cotinine levels) are shown in italics.

[2] Percentage of total ETS-attributable lung cancer deaths (3,570; *2,670*) in parentheses.

[3] NS = never-smokers; FS = former smokers who have quit 5+ years ago.

(3,060), the net effect is an increase of 12% to 3,570 at Z = 2.0, and a decrease of 13% to 2,670 when Z = 2.6. (FONT is the largest study and therefore the dominant influence in the combined relative risk from the 11 U.S. studies [RR_2 = 1.19], so the outcomes being compared here with those in Section 6.3.3 are not independent. Similarly, the Z-value of 1.75 used with RR_2 = 1.19 in the first analysis is subjectively based on the outcomes of several U.S. cotinine studies, including the FONT cotinine results.) Overall, these two analyses support an estimate in the neighborhood of 3,000 total lung cancer deaths in never-smokers and former smokers (quitters of 5+ years) from exposure to ETS in the United States for 1985.

The 3,000 figure is a composite value from estimates of varying degrees of uncertainty. The confidence for the female never-smoker estimates is highest. The lung cancer estimates for never-smoking females from exposure to spousal ETS (470 to 660; from Tables 6-2 and 6-4) are based on the direct evidence from epidemiologic studies and require the fewest assumptions. Adding in a figure for exposure to background ETS in never-smoking females (680 to 1,100) is subject to the assumptions and other uncertainties attached to the estimate of the parameter Z. The relative risk from ETS exposure, which depends on the risk from background sources of lung cancer as well as the risk from ETS, may differ in females and males. Consequently, the absolute risk (LCMR) in never-smoking females was assumed to apply to never-smoking males, adding 390 to 560 to the total (80 to 110 for spousal ETS and 280 to 450 for background ETS; Tables 6-3 and 6-5). Males, however, are thought to have higher background exposures to ETS than females, so this assumption is likely to underestimate the ETS-attributable lung cancer mortality in males.

The confidence in the estimates for former smokers is less than in those for never-smokers. These estimates also are probably low because they assume that ETS-attributable rates in never-smokers and former smokers are the same. Figures for lung cancer mortality from ETS in former smokers, for the same categories as never-smokers (i.e., females and males, background and spousal ETS), account for an additional 940 to 1,250 (totals of 310 to 440 for spousal ETS and 500 to 810 for background ETS, for both sexes). These figures for former smokers are summed from appropriate entries in Tables 6-3 and 6-5 (Tables 6-2 and 6-4 do not make them explicit; they are accounted for in the entry for lung cancer attributable to ever-smoking).

Finally, there is statistical uncertainty in each of the LCD estimates resulting from sampling variations around all of the parameter estimates that were used in the calculations. It is already apparent that the estimate of total lung cancer mortality attributable to ETS is sensitive to the values of Z and RR_2. Uncertainties associated with the parameter values assumed and the sensitivity of the estimated total ETS-attributable LCDs to various parameter values are examined next.

6.3.5. Sensitivity to Parameter Values

The estimates for ETS-attributable lung cancer mortality are clearly sensitive to the studies, methodology, and choice of models used, and previous methodologies have been presented in Section 6.2. Even for this current model, however, estimates will vary with different input values. Specifically, the estimates depend on the parameter values assumed for the total number of lung cancer deaths from all sources (T), the population size (N), the proportion of ever-smokers in the population (P_1), the proportion of never-smokers exposed to spousal ETS (P_2), the risk of ever-smokers relative to never-smokers (RR_1), the risk of never-smokers exposed to spousal ETS relative to unexposed never-smokers (RR_2), and the ratio of ETS exposure from spousal smoking and background (i.e., nonspousal) sources to background sources alone (Z).

The effects of changing several of the parameters is readily discernible. A change in T/N produces a proportional change in the same direction for all estimates of attributable mortality. A change in P_1 creates a proportional change in the same direction in all mortality figures for ever-smokers and a change in the opposite direction proportional to $1 - P_1$ in all estimates for never-smokers. The parameter values assumed for these three parameters are from the sources described in the preceding text and are assumed to be acceptably accurate. The value of P_2 is assumed to be 0.6, but values between 0.5 and 0.7 are easily credible. At either of those extremes, there is a 17% change in the lung cancer mortality due to spousal smoking, which only amounts to 80 for the first analysis (Table 6-2) and 100 for the second one (Table 6-4). The impact of changing RR_1, RR_2, or Z on the total lung cancer mortality attributable to ETS from the first analysis is displayed in Table 6-6 for RR_1 from 8 to 11, for RR_2 between 1.04 and 1.35 (extremes of the 90% confidence intervals for the 11 U.S. studies; Table 5-17), and for Z in the range 1.5 to 3.0.

For RR_1 in the interval (8,11), the total lung cancer mortality from ETS ranges from about 2,600 to 3,500, a 14% change in either direction relative to the comparison total of 3,060. The extremes are much greater over the range of values considered for RR_2 (1.04 to 1.35). At the low end, where the excess relative risk from spousal ETS is only 4%, there is a 77% decrease in the total lung cancer mortality to 700. The percentage change is roughly equivalent in the opposite direction when the excess relative risk is at the maximum value 35%, for a total of 5,190. The total is also highly sensitive to the value of Z. A decrease of only 0.25 from the comparison value of Z = 1.75 increases the total by 36% to 4,160. A 36% decrease in ETS-attributable mortality occurs at Z = 2.5, leaving a corresponding estimate of 1,950. At Z = 3.0, the total drops further to 1,680, a 45% decrease.

Varying more than one parameter value simultaneously may have a compounding or canceling effect on the total lung cancer mortality due to ETS. For example, at the following

Table 6-6. Effect of single parameter changes on lung cancer mortality due to ETS in never-smokers and former smokers who have quit 5+ years

Parameter change		LCM due to ETS			
		Background[1]	Spousal[2]	Total	Percentage of change[3]
None[4]		**2,210**	**850**	**3,060**	**0**
Z =	1.50	3,310	850	4,160	+36
	1.75	**2,210**	**850**	**3,060**	**0**
	2.00	1,660	850	2,510	-18
	2.25	1,320	850	2,170	-29
	2.50	1,100	850	1,950	-36
	2.75	950	850	1,800	-41
	3.00	830	850	1,680	-45
RR_2 =	1.04	510	190	700	-77
	1.05	630	240	870	-72
	1.10	1,220	470	1,690	-45
	1.15	1,780	690	2,470	-19
	1.19	**2,210**	**850**	**3,060**	**0**
	1.20	2,310	890	3,200	+5
	1.25	2,820	1,080	3,900	+27
	1.30	3,290	1,270	4,560	+49
	1.35	3,750	1,440	5,190	+70
RR_1 =	8.00	2,510	970	3,480	+14
	8.50	2,380	920	3,300	+8
	9.00	2,260.	870	3,130	+3
	9.26	**2,210**	**850**	**3,060**	**0**
	9.50	2,160	830	2,990	-2
	10.00	2,060	800	2,860	-7
	10.50	2,020	780	2,800	-9
	11.00	1,890	730	2,620	-14

[1] 69,100,000 at risk.
[2] 35,400,000 at risk.
[3] Percentage of change from total shown in boldface (the outcome from Tables 6-2 and 6-3, using the 11 U.S. studies).
[4] $Z = 1.75$, $RR_2 = 1.19$, $RR_1 = 9.26$.

values of RR_2, the range of percentage changes from the total of 3,060 ETS-attributable lung cancer deaths for values of Z in the interval 1.50 to 3.0 are shown in parentheses: $RR_2 = 1.04$ (-69%, -88%), $RR_2 = 1.15$ (+10%, -56%), $RR_2 = 1.25$ (+73%, -30%), and $RR_2 = 1.35$ (+131%, -7%). The total ETS-attributable LCD estimates range from 380 (at $RR_2 = 1.04$, $Z = 3.0$) to 7,060 (at $RR_2 = 1.35$, $Z = 1.5$). Without considering the additional variability that other parameters might add, it is apparent that the estimated lung cancer mortality from ETS is very sensitive to the parameters RR_2 and Z and that the uncertainty in these parameters alone leaves a fairly wide range of possibilities for the true population risk.

While various extreme values of these parameters can lead to the large range of estimates noted, the extremities of this range are less likely possibilities for the true population risk because the parameters RR_2 and Z are not actually independent and would be expected to co-vary in the same direction, not in the opposite direction as expressed by the extreme values. For example, if the contributions of background to total ETS exposure decrease, Z would increase, and the observable relative risk from spousal exposure, RR_2, would be expected to increase as well. In addition, most of the evidence presented in this report suggests that a narrower range of both RR_2 and Z are appropriate. Thus, while substantially higher or lower values are conceivable, this report concludes that the estimate of approximately 3,000 ETS-attributable LCDs based on the 11 U.S. studies is a reasonable one. Furthermore, this estimate is well corroborated by the estimates of 2,700 and 3,600 calculated by analyzing the FONT data alone, the only study dataset from which estimates of both RR_2 and Z are obtainable.

6.4. SUMMARY AND CONCLUSIONS ON POPULATION RISK

Having concluded in the previous chapter that ETS is causally associated with lung cancer in humans and belongs in EPA Group A of known human carcinogens, this chapter assesses the magnitude of that health impact in the U.S. population. The ubiquity of ETS in a typical individual's living environment results in the respiratory uptake of tobacco smoke to some degree in a very high percentage of the adult population, conservatively upwards of 75% based on the outcome of urinary cotinine/creatinine studies in nonsmokers. Compared with observations on active smokers, body cotinine levels in nonsmokers are low, on the order of a few percent, and there is considerable variability in interindividual metabolism of nicotine to cotinine. Some authors have used the relative cotinine levels in active and passive smokers to estimate the probability of lung cancer in nonsmokers by extrapolating downward on a dose-response curve for active smokers. This "cigarette-equivalents" approach requires several assumptions, e.g., that the dose-response curve used for active smokers is reasonably accurate and low-dose extrapolation of risk for active smokers is credible, that cotinine is proportional (and hence a substitute for) whatever is used for "dose" in the dose-response curve, and that the risk calculated in this way applies equally to active and passive smokers with equivalent cotinine measures. The effect of differences in physico-chemical properties of mainstream smoke and sidestream smoke (the principal component of ETS), in lung dosimetry between active and passive smoking, and in exposure patterns (related to concentration and duration of exposure) are not fully understood, but the current state of knowledge casts doubts on the validity of these assumptions.

The remaining approach to population risk extrapolates to the general population from the epidemiologic evidence of increased relative risk of lung cancer in never-smoking women married to smokers. To extrapolate exposure and consequent risk to other sources of ETS exposure, cotinine levels of never-smokers exposed to spousal ETS are compared with those of never-smokers exposed only to other sources of ETS (background), and it is assumed that excess risks of lung cancer from ETS exposures, using cotinine levels as a surrogate measure, are proportional to current ETS exposure levels. (Here, cotinine levels are used to gauge relative levels of *ETS* exposure, not to extrapolate between active and passive smoking as in the "cigarette-equivalents" approach.) The use of current cotinine data to estimate ETS exposure in nonsmokers seems reasonable because cotinine levels correlate quite well with questionnaire response on ETS exposure. However, the total estimate of population risk is sensitive to uncertainty in making these assumptions and variability in the use of cotinine measures.

This report uses the modeling approach based on direct ETS epidemiologic evidence because the assumptions are fewer and more valid than for the "cigarette-equivalents" approach, and the abundance of human data from actual environmental exposures makes this preferred approach feasible. The total number of lung cancer deaths in U.S. females from all causes is partitioned into components attributable to non-tobacco-smoke-related causes (background causes unrelated to active or passive smoking), background ETS (also called nonspousal ETS), spousal ETS, and ever-smoking. Two sets of calculations are made for the U.S. female population age 35 and over in 1985 based on parameter values from national statistics and estimates from the epidemiologic studies on ETS and lung cancer. They differ in the values assumed for two parameters in the formulae for attributable risk: RR_2, the relative risk of lung cancer for never-smokers exposed to spousal smoke, and Z, the ratio of cotinine concentrations in never-smokers exposed to spousal ETS to those exposed to background ETS only. The first analysis uses the pooled estimate of RR_2 from the 11 U.S. studies from Chapter 5, and a subjective value of Z based on the outcomes of independent U.S. cotinine studies ($RR_2 = 1.19$ and $Z = 1.75$). The second analysis uses the estimates of RR_2 and Z from the large, high-quality Fontham et al. study

(1991), the sole U.S. study that collected cotinine data for its study population (RR_2 = 1.28 with mean Z = 2.0 and with median Z = 2.6).

The estimated lung cancer mortality in never-smoking women from ETS (background and spousal ETS) is 1,500 in the first analysis and 1,760 (1,340) in the second analysis for Z = 2.0 (2.6). When estimates for never-smoking males and former smokers (5+ year quitters) of both sexes are added, the corresponding totals are 3,060 and 3,570 (2,670). All of these figures are based on calculations in which unknown parameter values are replaced with numerical estimates that are subject to uncertainty, and departures in either direction cannot be precluded as unrealistic possibilities for the correct population risks. Nonetheless, because of the large database utilized and the extensive analysis performed, there is a high degree of confidence in the estimates derived for female never-smokers. The figures for male never-smokers and former smokers of both sexes are subject to more uncertainty because more assumptions were necessary for extrapolation from the epidemiologic results. The estimates for male never-smokers, in particular, may be on the low side because males generally are exposed to higher levels of background ETS than females. In summary, our analyses support a total of approximately 3,000 as an estimate for the annual U.S. lung cancer deaths in nonsmokers attributable to ETS exposure.

A quantitative estimate of the variance associated with the 3,000 estimate is not possible without many assumptions, both about the model and the accuracy of the parameters used to derive the population estimates. As exhibited in Table 6-6, we believe the largest variability to be associated with RR_2 and Z. Based on the statistical variations, estimates as low as 400 and as high as 7,000 are possible. However, where specific assumptions were made, we believe that they are generally conservative, and we expect that the actual number may be greater than 3,000.

A feature of variability not addressed in the range presented above is the correlation between RR_2 and Z. The greater the correlation, the smaller will be the expected variance of RR_{02}, resulting in a narrower range of lung cancer estimates. Because only one lung cancer study, FONT, allows RR_2 and Z to be jointly estimated, no assessment of this correlation is possible. However, the two point estimates derived from the FONT data--2,700 and 3,600--provide additional reassurance in the 3,000 estimate.

In conclusion, despite some unavoidable uncertainties, we believe these estimates of ETS-attributable lung cancer mortality to be fairly reliable, if not conservatively low, especially with respect to the male nonsmoker component. First, the weight of evidence that ETS is a human lung carcinogen is very strong. Second, the estimates are based on a large amount of data from various studies of human exposures to actual environmental levels of ETS. They do not suffer from a need to extrapolate from an animal species to humans or from high to low exposures, as is nearly always the case in environmental quantitative health risk assessment. Thus, the confidence in these estimates is judged to be medium to high. In summary, the evidence demonstrates that ETS has a very substantial and serious public health impact.

7. PASSIVE SMOKING AND RESPIRATORY DISORDERS OTHER THAN CANCER

7.1. INTRODUCTION

In 1984, a report of the Surgeon General identified cigarette smoking as the major cause of chronic obstructive lung disease in the United States (U.S. DHHS, 1984). The same report stated that there is conclusive evidence showing that smokers are at increased risk of developing respiratory symptoms such as chronic cough, chronic phlegm production, and wheezing (U.S. DHHS, 1984). More recently, longitudinal studies have demonstrated accelerated decline in lung function in smoking adults (Camilli et al., 1987). In children and adolescents who have recently taken up smoking, several cross-sectional studies have found statistically significant increases in the prevalence of respiratory symptoms (cough, phlegm production, and dyspnea [i.e., shortness of breath]) (Seely et al., 1971; Bewley et al., 1973). Longitudinal studies also have demonstrated that, among young teenagers, functional impairment attributable to smoking may be found after as little as 1 year of smoking 10 or more cigarettes per week (Woolcock et al., 1984).

From a pathophysiologic point of view, smoking is associated with significant structural changes in both the airways and the pulmonary parenchyma (U.S. DHHS, 1984). These changes include hypertrophy and hyperplasia of the upper airway mucus glands, leading to an increase in mucus production, with an accompanying increased prevalence of cough and phlegm. Chronic inflammation of the smaller airways leads to bronchial obstruction. However, airway narrowing also may be due to the destruction of the alveolar walls and the consequent decrease in lung elasticity and development of centrilobular emphysema (Bellofiore et al., 1989). Smoking also may increase mucosal permeability to allergens. This may result in increased total and specific IgE levels (Zetterstrom et al., 1981) and increased blood eosinophil counts (Halonen et al., 1982).

The ascertained consequences of active smoking on respiratory health, and the fact that significant effects have been observed at relatively low-dose exposures, lead to an examination for similar effects with environmental tobacco smoke (ETS). Unlike active smoking, involuntary exposure to ETS (or "passive smoking") affects individuals of all ages, particularly infants and children. An extensive analysis of respiratory effects of ETS in children suggests that the lung of the young child may be particularly susceptible to environmental insults (NRC, 1986). Exposures in early periods of life during which the lung is undergoing significant growth and remodeling may alter the pattern of lung development and increase the risk for both acute and chronic respiratory illnesses.

Acute respiratory illnesses are one of the leading causes of morbidity and mortality during infancy and childhood. One-third of all infants have at least one lower respiratory tract illness (bronchitis, bronchiolitis, croup, or pneumonia) during the first year of life (Wright et al., 1989), whereas approximately one-fourth have these same illnesses during the second and third years of life (Gwinn et al., 1991). The high incidence of these potentially severe illnesses has an important consequence from a public health viewpoint: Even small increases in risk due to passive exposure to ETS would considerably increase the absolute number of cases in the first 3 years of life (see Chapter 8). In addition, several studies have shown that lower respiratory tract illnesses occurring early in life are associated with a significantly higher prevalence of asthma and other chronic respiratory diseases and with lower levels of respiratory function later in life (reviewed extensively by Samet and collaborators [1983]).

This chapter reviews and analyzes epidemiologic studies of noncancer respiratory system effects of passive smoking, starting with possible biological mechanisms (Section 7.2). The evidence indicating a relationship between exposure to ETS during childhood and acute respiratory illnesses (Section 7.3), middle ear diseases (Section 7.4), chronic respiratory symptoms (Section 7.5), asthma (Section 7.6), sudden infant death syndrome (Section 7.7), and lung function impairment (Section 7.8) is evaluated. Passive smoking as a risk factor for noncancer respiratory illnesses and lower lung function in adults also is analyzed (Section 7.9). A health hazard assessment and population impact is presented in the next chapter.

7.2. BIOLOGICAL MECHANISMS

7.2.1. Plausibility

It is plausible that passive smoking may produce effects similar to those known to be elicited by active smoking. However, several differences both between active and passive forms of exposure and among the individuals exposed to them need to be considered.

The concentration of smoke components inhaled by subjects exposed to ETS is small compared with that from active smoking. Therefore, effect will be highly dependent on the nature of the dose-response curve (NRC, 1986). It is likely that there is a distribution of susceptibility to the effects of ETS that may depend on, among other factors, age, gender, genetic predisposition, respiratory history, and concomitant exposure to other risk factors for the particular outcome being studied. The ability to ascertain responses to very low concentrations also depends on the reliability and sensitivity of the instruments utilized.

Breathing patterns for the inhalation of mainstream smoke (MS) and ETS differ considerably; active smokers inhale intensely and intermittently and usually hold their breath for some time at the end of inspiration. This increases the amount of smoke components that are deposited and absorbed (U.S. DHHS, 1986). Passive smokers inhale with tidal breaths and continuously. Therefore, patterns of particle deposition and gas diffusion and absorption differ considerably for these two types of inhalation.

There are also important differences in the physicochemical properties of ETS and MS (see Chapter 3). These have been extensively reviewed earlier by the National Research Council (NRC, 1986) and the Surgeon General (U.S. DHHS, 1986). ETS is a combination of exhaled MS, sidestream smoke (that is, the aerosol that is emitted from the burning cone between puffs), smoke emitted from the burning side of the cigarette during puffs, and gases that diffuse through the cigarette paper into the environment. This mixture may be modified by reactions that occur in the air before involuntary inhalation. This "aging" process includes volatilization of nicotine, which is present in the particulate phase in MS but is almost exclusively a component of the vapor phase of ETS. Aging of ETS also entails a decrease in the mean diameter of its particles from 0.32 μm to 0.1-0.14 μm, compared to a mean particle diameter for MS of 0.4 μm (NRC, 1986).

Individual and socioeconomic susceptibility may be important determinants of possible effects of ETS on respiratory health. A self-selection process almost certainly occurs among subjects who experiment with cigarettes, whereby those more susceptible to the irritant or sensitizing effects of tobacco smoke either never start or quit smoking (the so-called "healthy smoker" effect). Infants, children, and nonsmoking adults thus may include a disproportionate number of susceptible subjects when compared with smoking adults. In addition, recent studies clearly have shown that, as incidence and prevalence of cigarette smoking has decreased, the socioeconomic characteristics of smokers also have changed. Among smokers, the proportion of subjects of lower educational level has increased in the past 20 years (Pierce et al., 1989). The female-to-male ratio also has increased (Fiore et al., 1989), and this is particularly true for young, poor women, in whom incidence and prevalence of smoking has increased (Williamson et al., 1989). It is thus possible that exposure to ETS may be most prevalent today among precisely those infants and children who are known to be at a high risk of developing respiratory illnesses early in life.

7.2.2. Effects of Exposure In Utero and During the First Months of Life

A factor that may significantly modify the effect of passive smoking (particularly in children) is exposure to tobacco smoke components by the fetus during pregnancy. This type of exposure differs considerably from passive smoking; in fact, the fetus (including its lungs) is exposed to components of tobacco smoke that are absorbed by the mother and that cross the placental barrier, whereas passive smoking directly affects the bronchial mucosa and the alveolus. It is difficult to distinguish between the possible effects of smoking during pregnancy and those of ETS exposure after birth. Some women may quit smoking during pregnancy, only to resume after pregnancy is over. Most mothers who smoke during pregnancy continue smoking after the birth of their child (Wright et al., 1991), and among those who stop smoking after birth, the influence on that decision of events occurring shortly after birth (such as respiratory illnesses in their child) cannot be excluded. Recall bias also may influence the results of retrospective studies claiming differential effects on lung function of prenatal and postnatal maternal smoking habits (Yarnell and St. Leger, 1979).

To attempt to circumvent these problems, researchers have studied infant lung function shortly after birth (the youngest group of infants reported was 2 weeks old [Neddenriep et al., 1990]), with the implication that subsequent changes encountered could be attributed mainly to ETS exposure. However, the possibility that even brief exposure to ETS may affect the lungs at a highly susceptible age may not be discarded. Maternal smoking during pregnancy needs to be considered, therefore, as a potential modifier of the effect of passive smoking on respiratory health, particularly in children.

Exposure to compounds present in tobacco smoke may affect the fetal and neonatal lung and alter lung structure much like these same compounds do in smoking adults. Neddenriep and coworkers (1990) studied 31 newborns and reported that those whose mothers smoked during pregnancy had significant increases in specific lung compliance (i.e., lung compliance/lung volume) at 2 weeks of age when compared with infants of nonsmoking mothers. The authors concluded that exposure to tobacco products detrimentally affects the elastic properties of the fetal lung. Although these effects also could be attributed to postnatal exposure to ETS, it is unlikely that such a brief period of postnatal exposure would be responsible for these changes affecting the lung parenchyma (U.S. DHHS, 1986).

There is evidence for similar effects of prenatal lung development in animal models. Collins and associates (1985) exposed pregnant rats to MS during day 5 to day 20 of gestation. They found that pups of exposed rats showed reduced lung volume, reduced number of lung saccules, and reduced length of elastin fibers in the lung interstitium. This apparently resulted in a decrease in lung elasticity: For the same inflation pressure, pups of exposed mothers had significantly higher weight-corrected lung volumes than did pups of unexposed mothers. Vidic and coworkers (1989) exposed female rats for 6 months (including mating and gestation) to MS. They found that lungs of their 15-day-old pups had less parenchymal tissue, less extracellular matrix, less collagen, and less elastin than found in lungs of control animals. This may explain the increased lung compliance observed by Collins et al. (1985) in pups exposed to tobacco smoke products in utero.

Hanrahan and coworkers (1990) reported that infants born to smoking mothers had significantly reduced levels of forced expiratory flows. The researchers studied 80 mother/child pairs and found significant correlations between the cotinine/creatinine ratio in urine specimens obtained during pregnancy in the mother and maximal expiratory flows and tidal volumes at a postconceptional age of 50 weeks or younger in their children. The investigators concluded that exposure due to prenatal smoking diminishes infant pulmonary function at birth and, by inference, airway size. These authors also measured maximal flows during tidal breathing in their subjects. At rather low lung volumes, such as those present during tidal breathing, airway size and maximal flows are both a function of lung elasticity. These results thus may be due to both a specific alteration of the infant's airways and an increased lung compliance in infants whose lungs are small relative to the infant's length.

It also has been suggested that the increased IgE levels observed in adult smokers also may be present in fetuses whose mothers smoke during pregnancy. Magnusson (1986) reported that cord serum levels of IgE and IgD were significantly higher for neonates whose mothers smoked during pregnancy, particularly if the neonates had no parental history of allergic disorders. Cord serum levels of IgD (but not of IgE) were increased for neonates whose fathers smoked, and this effect was independent of maternal smoking. A more recent study on a larger sample (more than 1,000 neonates) failed to find any significant difference in cord serum IgE levels between infants (N = 193) of mothers who smoked during pregnancy and those (N = 881) of mothers who did not (Halonen et al., 1991).

It also has been reported recently that the pulmonary neuroendocrine system may be altered in infants whose mothers smoke during pregnancy. The pulmonary neuroendocrine system, located in the tracheobronchial tree, consists of specialized cells (isolated or in clusters called "neuroepithelial bodies") that are closely related to nerves. In humans, these cells increase in number significantly during intrauterine development, reach a maximum around birth, and then rapidly decline during the first 2 years of life. Their function is not well understood, but the presence of potent growth factors and bronchoconstrictive substances in their granules suggests that they play an important role in growth regulation and airway tone control during this period of lung development (Stahlman and Gray, 1984). Chen and coworkers (1987) reported that maternal smoking during pregnancy increases the size of infant lung neuroepithelial bodies and decreases the amount of core granules present in them. Wang and coworkers (1984) had reported previously that mother mice receiving tap water with nicotine during pregnancy and during lactation had offspring with increased numbers of neuroepithelial bodies at 5 days of age when compared with baby mice whose mothers were not exposed. Baby mice exposed to nicotine only during pregnancy had neuroepithelial bodies of intermediate size with respect to these two groups, whereas those exposed only during lactation had neuroepithelial bodies of normal size. By age 30 days, only baby mice exposed to nicotine during both pregnancy and lactation had neuroepithelial bodies that were larger than those of control animals.

Activation of the pulmonary neuroendocrine system is not limited to ETS exposure; it is activated by active smoking as well. Aguayo and collaborators (1989) reported that bronchoalveolar lavage fluids obtained from healthy smokers have increased levels of bombesin-like peptides, which are a normal component and a secretion product of human lung neuroendocrine cells (Cutz et al., 1981).

In summary, effects of maternal smoking during pregnancy on the fetus are difficult to distinguish from those elicited by early postnatal exposure to ETS. Animal studies suggest that postnatal exposure to tobacco products enhances the effects of in utero exposure to these same products.

7.2.3. Long-Term Significance of Early Effects on Airway Function

By altering the structural and functional properties of the lung, prenatal exposure to tobacco smoke products and early postnatal exposure to ETS increase the likelihood of more severe complications during viral respiratory infections early in life. Martinez and collaborators (1988a) measured lung function before 6 months of age and before any lower respiratory illness in 124 infants. They found that infants with the lowest levels for various indices of airway size were three to nine times more likely to develop wheezing respiratory illnesses during the first year of life than the rest of the population. The same authors (Martinez et al., 1991) subsequently showed that, in these same infants with lower initial levels of lung function, recurrent wheezing illnesses also were more likely to occur during the first 3 years of life. A similar study performed in Australia (Young et al., 1990) confirmed that infants who present episodes of coughing and wheezing during the first 6 months of life have lower maximal expiratory flows before any such illnesses develop.

The increased likelihood of pulmonary complications during viral respiratory infections in infants of smoking parents has important long-term consequences for the affected individual. There is considerable evidence suggesting that subjects with chronic obstructive lung diseases have a history of childhood respiratory illnesses more often than subjects without such diseases (reviewed by Samet and coworkers [1983]). Burrows and collaborators (1988) found that active smokers without asthma (N = 41) who had a history of respiratory troubles before age 16 years showed significantly steeper declines in FEV_1 (as a percentage of predicted) after the age of 40 than did nonasthmatic smokers without such a history (N = 396). Although these results may have been influenced by recall bias, they suggest that lower respiratory tract illnesses during a period of rapid lung development may damage the lung and increase the susceptibility to potentially harmful environmental stimuli.

There is no information available on the degree of reversibility of changes induced by exposure to ETS during early life. Longitudinal studies of lung function in older children have shown, however, that diminished levels of lung function are found in children of smoking parents at least until the adolescent years.

7.2.4. Exposure to ETS and Bronchial Hyperresponsiveness

Bronchial hyperresponsiveness consists of an enhanced sensitivity of the airways to pharmacologic or physical stimuli that normally produce no changes or only small decreases in lung function in normal individuals. Subjects with bronchial hyperresponsiveness have significant drops in airway conductance and maximal expiratory flows after inhalation of stimuli such as cold air, hypertonic saline, nebulized distilled water, methacholine, or histamine. Bronchial hyperresponsiveness is regarded as characteristic of asthma (O'Connor et al., 1989) and may precede the development of this disease in children (Hopp et al., 1990). It has also been considered as a predisposing factor for chronic airflow limitation in adult life (O'Connor et al., 1989).

Recent studies of large population samples have shown that active smokers have increased prevalence of bronchial hyperresponsiveness (Woolcock et al., 1987; Sparrow et al., 1987; Burney et al., 1987) when compared with nonsmokers. This relationship seems to be independent of other possible determinants of bronchial hyperresponsiveness (O'Connor et al., 1989). However, one large study of almost 2,000 subjects from a general population sample failed to find a significant relationship between smoking and prevalence of bronchial hyperresponsiveness (Rijcken et al., 1987). The subjects involved in the latter study were younger and were therefore exposed to a smaller average cumulative pack-years of smoking than were the subjects of studies in which a positive relationship was found. This suggests that the relationship may be evident only among individuals with a high cumulative exposure.

Epidemiologic studies have demonstrated that exposure to ETS is associated with an increased prevalence of bronchial hyperresponsiveness in children. Murray and Morrison (1986), in a cross-sectional study, reported that asthmatic children of smoking mothers were four times more likely to show increased responsiveness to histamine than were asthmatic children of nonsmoking mothers. O'Connor and coworkers (1987), in a study of a general population sample, found a significant association between maternal smoking and bronchial hyperresponsiveness (as assessed with eucapnic hyperpnea with subfreezing air) among asthmatic children, but not among nonasthmatic children (Weiss et al., 1985). Martinez and coworkers (1988b) reported a fourfold increase in bronchial responsiveness to carbachol among male children of smoking parents when compared with male children of parents who were both nonsmokers. A smaller (and statistically not significant) increase in bronchial responsiveness was reported in girls. These authors also found that the effect of parental smoking was stronger in asthmatic children, and results were still significant after controlling for this factor in a multivariable analysis. Because only a small proportion of mothers in this population smoked during pregnancy, the effect was considered to be associated mainly with exposure to ETS in these children. Lebowitz and Quackenboss (1990) showed that odds of having bronchial reactivity (as assessed by the diurnal variability in maximal expiratory flow rate) were 3.6 times as high among 18 children aged 15 years and younger who lived with persons who smoked more than 20 cigarettes per day than among 62 children of the same age who lived with nonsmokers (95% C.I. = 1.2, 10.6). Children living with smokers of 1 to 20 cigarettes per day had a prevalence of bronchial reactivity that was similar to that of children living with nonsmokers.

Therefore, there is evidence indicating that parental smoking enhances bronchial responsiveness in children. The mechanism for this effect and the possible role of atopy in it are unknown. The doses required to enhance bronchial responsiveness in children exposed to ETS are apparently much lower than those required to elicit similar effects among adult active smokers. A process of self-selection, by which adults who are more sensitive to the effects of tobacco smoke do not start smoking or quit smoking earlier, may explain this finding. Variations in bronchial responsiveness with age also may be involved (Hopp et al., 1985).

Increased bronchial responsiveness may be an important predisposing factor for the development of asthma in childhood (Hopp et al., 1990). Moreover, it has been suggested that bronchial hyperresponsiveness may have effects on the developing respiratory system that predispose to chronic obstructive lung disease in later life (O'Connor et al., 1989). Redline et al. (1989) examined bronchial responsiveness to hyperventilation with cold air and its association with growth of lung function over a 12-year period in 184 children and young adults (aged 8 to 23 years) over a maximum span of 12 years. Among subjects with persistent positive responses to cold air during followup, forced vital capacity grew faster, but forced expiratory flows grew more slowly, than among subjects who consistently did not respond to cold air. Among subjects with intermittently positive cold air responses, forced expiratory flows also grew more slowly than in controls, but growth of forced vital capacity was not changed. Although this study needs confirmation, its results suggest that bronchial hyperresponsiveness may have significant effects on the rate of growth of airway function and lung size in children.

7.2.5. ETS Exposure and Atopy

Atopy has been defined epidemiologically as the presence of immediate hypersensitivity to at least one potential allergen administered by skin prick test. Atopy is an immediate form of hypersensitivity to antigens (called allergens) that is mediated by IgE immunoglobulin. Allergy (as indicated by positive skin test reactivity to allergens, high levels of circulating IgE, or both) is known to be present in almost all cases of childhood asthma. Recent epidemiologic studies have indicated that an IgE-mediated reaction may be necessary for the occurrence of almost all cases of asthma at any age (Burrows et al., 1989).

Although genetic factors appear to play a major role in the regulation of IgE production (Meyers et al., 1987; Hanson et al., 1991), several reports have indicated that active smoking significantly increases total serum IgE concentrations and may thus influence the occurrence of allergy (Gerrard et al., 1980; Burrows et al., 1981; Zetterstrom et al., 1981; Taylor et al., 1985). Active smokers also have been found to have higher eosinophil counts and increased prevalence of eosinophilia when compared with nonsmokers (Kauffmann et al., 1986; Halonen et al., 1982; Taylor et al., 1985). The physical and chemical similarities between MS and ETS have prompted the investigation of a possible role of passive smoking in allergic sensitization in children.

Weiss and collaborators (1985) first reported a 2.2-fold increased risk of being atopic in children of smoking mothers. Martinez and coworkers (1988b) confirmed that children of smoking parents were significantly more likely to be atopic than were children of nonsmoking parents, and the researchers reported that this association was stronger for male children. They also found a rough dose-response relationship between the number of cigarettes smoked by parents and the intensity of the skin reactions to a battery of allergens. Ronchetti and collaborators (1990) extended these findings in the same population sample of Martinez and coworkers. They found that total serum IgE levels and eosinophil counts were significantly increased in children of smoking parents, and the effect was related to both maternal and paternal smoking.

It is relevant to note that, due to the so-called "healthy smoker effect," children of smokers should be genetically less sensitive than children of nonsmokers, because the latter are likely to include a disproportionate number of allergic subjects who are very sensitive to the irritant effects of smoke. As a consequence, the atopy-inducing effects of ETS may be substantially underestimated.

In summary, there is convincing evidence that both maternal smoking during pregnancy and postnatal exposure to ETS alter lung function and structure, increase bronchial responsiveness, and enhance the process of allergic sensitization. These changes elicited by exposure to tobacco products may predispose children to lower respiratory tract illnesses early in life and to asthma, lower levels of lung function, and chronic airflow limitation later in life. Most of these same effects have been described for active smoking in adults. These smoke-induced changes are, therefore, known biological mechanisms for the increased prevalence of respiratory diseases associated with ETS exposure described later in this chapter.

Exposure to tobacco smoke products during pregnancy and to ETS soon after birth may be the most important preventable cause of early lung and airway damage leading to both lower respiratory illness in early childhood and chronic airflow limitation later in life.

7.3. EFFECT OF PASSIVE SMOKING ON ACUTE RESPIRATORY ILLNESSES IN CHILDREN

A review of the literature that examined the effects of exposure to ETS on the acute respiratory illness experiences of children was contained in the Surgeon General's report on the health consequences of involuntary smoking (U.S. DHHS, 1986) and in the report on environmental tobacco smoke by the NRC (1986). Table 7-1 shows the studies referenced in these two reports.

The Surgeon General's report concluded that "the results of these studies show excess acute respiratory illness in children of parents who smoke, particularly in children under 2 years of age," and that "this pattern is evident in studies conducted with different methodologies and in different locales" (page 44). It estimated that the increased risk of hospitalization for severe bronchitis or pneumonia ranged from 20% to 40% during the first year of life. The report stated that "young children appear to be a more susceptible population for the adverse effects of involuntary smoking than older children and adults" (page 44). Finally, the report suggested that "acute respiratory illnesses during childhood may have long-term effects on lung growth and development, and might increase the susceptibility to the effects of active smoking and to the development of chronic lung disease" (page 44).

The 1986 NRC report observed that "all the studies that have examined the incidence of respiratory illnesses in children under the age of 1 year have shown a positive association between such illnesses and exposure to ETS. The association is very unlikely to have arisen by chance" (page 208). It pointed out that "some of the studies have examined the possibility that the association is indirect by allowing for confounding factors . . . and have concluded that such factors do not explain the results. This argues, therefore, in favor of a causal explanation" (page 208). The report concluded that "bronchitis, pneumonia, and other lower-respiratory-tract illnesses occur up to twice as often during the first year of life in children who have one or more parents who smoke than in children of nonsmokers" (page 217).

Table 7-1. Studies on respiratory illness referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Cameron et al. (1969)	158	Children (6 to 9)	X	
Colley (1971)	2,205	Infants	X	
Colley (1974)	1,598	Children (6 to 14)		X
Dutau et al. (1981)	892	Infants/children (0 to 6)		X
Fergusson et al. (1981)	1,265	Infants	X	X
Leeder et al. (1976)	2,149	Infants	X	X
Pedreira et al. (1985)	1,144	Infants	X	X
Pullan and Hey (1982)	130	Children (10 to 11)	X	
Rantakallio (1978)	3,644	Infants/children (0 to 5)	X	X
Speizer et al. (1980)	8,120	Children (6 to 10)	X	X
Ware et al. (1984)	8,528	Children (5 to 9)	X	

7.3.1. Recent Studies on Acute Lower Respiratory Illnesses

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and acute lower respiratory illnesses in children (see Table 7-2).

Chen and coworkers (1986) studied 1,058 infants out of 1,163 infants born in a given period in two neighborhoods in Shanghai, People's Republic of China. Information on hospital admissions from birth to 18 months, smoking habits of household members, parental education, and social and living conditions was obtained by use of a self-administered questionnaire completed by the parents when the child reached 18 months of age. Hospital admissions were divided into those due to respiratory illness and those from all other conditions. None of the mothers in the study smoked. There was no statistically significant association between exposure to ETS and admission to the hospital for any condition other than respiratory illnesses. Compared with nonsmoking households, the risk of being admitted to a hospital for respiratory illnesses was 17% higher when one to nine cigarettes were smoked daily by household members (95% C.I. =

Table 7-2. Recent epidemiologic studies of effects of passive smoking on acute lower respiratory tract illnesses (LRIs)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Breese-Hall et al. (1984)	Cases: 29 infants hospitalized with bronchiolitis due to respiratory syncytial virus (RSV) Controls: 58 infants hospitalized for nonrespiratory conditions; 58 infants hospitalized due to LRIs not due to RSV	Parental questionnaire	See population studied	Cases vs. controls Odds ratio (OR) = 4.8 (1.8, 13.0) (>5 cig./day vs. none) LRI controls vs. non-LRI controls OR = 2.7 (1.3, 5.7)	Cases matched to controls for age, sex, race, month of admission, form of payment; selection bias not ruled out
Chen et al. (1986)	1,058 infants born in Shanghai, China	Parental self-administered questionnaire; number of cigarettes smoked by household members	Admissions to hospital for respiratory illness as reported by parents	Cig./day OR 1-9 1.2 (0.6, 2.3) >9 1.9 (1.1, 3.4)	Controlling for crowding, paternal education, feeding practices, birthweight, family history of chronic respiratory illness

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Chen et al. (1988)	2,227 infants born in Shanghai, China	Household self-administered questionnaire	Incidence of hospitalization for respiratory illness, incidence of bronchitis or pneumonia first 18 mo. of life	First 6 mo. of life: OR = 3.0 (1.6, 5.7); 7-18 mo. of life: OR = 1.8 (1.0, 3.2)	No smoking mothers; controlling for sex, birthweight, feeding practices, nursery care, paternal education, use of coal for cooking, family history of chronic respiratory illness
Chen (1989)	Same as above	Same as above	Same as above	First 18 mo. of life: incidence density ratio (IDR) = 1.6 for breast-fed babies; IDR = 3.4 for non-breast-fed babies; confidence intervals not calculable	

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986a)	53 infants with bronchiolitis; 106 controls	Parental questionnaire at mean age 8 yr.	See population studied	Cases vs. controls OR = 2.4 (1.2, 4.8) (smoking mother vs. nonsmoking mother)	Cases matched to controls for sex and age; controlling for family history of asthma, social status, older siblings, crowding; selection bias not ruled out
Ogston et al. (1987)	1,565 infants in New Zealand	Maternal and paternal smoking habits during pregnancy by questionnaire	Upper and lower respiratory illnesses during first year of life	Paternal smoking OR = 1.43 (1.05, 1.96); maternal smoking OR = 1.82 (1.25, 3.64)	Upper and lower respiratory illnesses not distinguished; controlling for maternal age, feeding practices, heating type, social class
Anderson et al. (1988)	102 children hospitalized in Atlanta, Georgia, <2 yr.; 199 controls	Self-reported smoking habits of family members	LRI	No effect of parental smoking after controlling for other risk factors	Selection bias possible

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Table 7-2. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Woodward et al. (1990)	2,125 children aged 18 mo. to 3 yr.	Self-administered mailed questionnaire	"Respiratory score" regarding 13 different symptoms; top 20% compared with low 20%	OR = 2.0 (1.3, 3.4) of having a smoking mother for high scores compared with low scores; no effect of paternal smoking	Controlling for parental history of respiratory illness, child care, parental occupation, maternal stress
Wright et al. (1991)	847 white children born in Tucson, Arizona	Self-administered questionnaire and cotinine levels in a subsample	LRIs as assessed by the infants' pediatricians	OR = 1.5 (1.1, 2.2) of having smoking mother; no effect of paternal smoking	Effects significant only for LRIs occurring in the first 6 mo. of life; controlling for day care, room sharing, parental history of respiratory illnesses, feeding practices, sex, and maternal education
Reese et al. (1992)	491 children aged 1 mo. to 17 yr.	Cotinine levels in urine of children; questionnaire of parents' current smoking	Hospitalization for bronchiolitis	Higher levels in children hospitalized for bronchiolitis than in controls ($p<0.02$)	No effects of ETS on hospitalization for asthma

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[1] 95% confidence intervals in parentheses.

0.6, 2.3) and was 89% higher when more than nine cigarettes were smoked daily by household members (95% C.I. = 1.1, 3.4). The authors controlled for the effects of crowding, chronic respiratory illness in the family, father's education, type of feeding, and birthweight.

Chen and coworkers (1988) subsequently studied 2,227 out of 2,315 children born in the last quarter of 1983 in Chang-Ning District, Shanghai, People's Republic of China. There were no smoking mothers in this population. The authors reported a significant linear relationship of total daily cigarette consumption by family members with incidence density of hospitalization for respiratory illness and with cumulative incidence of bronchitis and pneumonia in the first 18 months of life. The relationship was stronger for the 1- to 6-month period than for the 7- to 18-month period: When compared with households whose members did not smoke at home, the risk of being hospitalized for respiratory illness during the 1- to 6-month interval was three times as high (95% C.I. = 1.6, 5.7) in households whose members smoked more than nine cigarettes at home, whereas comparison of the same two types of household showed that the risk of being hospitalized for respiratory illness during the 7- to 18-month interval was only 1.8 times as high (95% C.I. = 1.0, 3.2) in the smoking household. The relationship also was stronger among low-birthweight infants. Results were independent of sex, birthweight, feeding practices, nursery care, paternal education, family history of chronic respiratory diseases, and use of coal for cooking.

In a different publication based on the same data from the 1988 study, Chen (1989) reported that the effects of passive smoking were stronger in artificially fed infants than in breast-fed infants. When comparing breast-fed infants of nonsmoking and smoking families, the risk of being hospitalized for respiratory illness in the first 18 months of life was 1.6 times as high for breast-fed infants of smoking families (> 19 cig./day), whereas the same risk was 3.4 times as high among non-breast-fed infants of smoking families.

The studies by Chen (1989) and Chen and coworkers (1986, 1988) were retrospective in nature and thus not immune to possible biases generated by the fact that the occurrence of the outcome event may enhance reporting or recall of the conditions considered as risk factors. However, conclusions are strengthened by the finding that admissions for nonrespiratory illnesses were unrelated to passive smoking in the study in which the relationship was assessed (Chen et al., 1986) and by the fact that the finding remained significant after adjusting for known confounders.

Breese-Hall and coworkers (1984) studied 29 infants hospitalized with confirmed RSV bronchiolitis before age 2, 58 controls hospitalized for acute nonrespiratory conditions, and 58 controls hospitalized for acute lower respiratory illnesses from causes other than RSV. Cases and controls were matched for age, sex, race, month of admission, and form of payment for hospitalization. Information on smoking habits in the family was obtained at the time of each patient's admission. Cases were 4.8 times as likely as controls (95% C.I. = 1.8, 13.0) to have one or more household members who smoked five or more cigarettes per day. However, there was no significant difference in the prevalence of cigarette smoking in the households of subjects with respiratory illnesses caused by RSV and those not caused by RSV. This was attributable to the fact that the controls with respiratory illnesses not caused by RSV were also much more likely to live with smokers of five or more cigarettes per day than were controls with nonrespiratory illnesses (OR = 2.7, 95% C.I. = 1.3, 5.7). Little information is given about enrollment and refusals; thus, it is not possible to know if selection bias may have influenced the results. Also, other possible confounders such as socioeconomic level were not taken into account when matching cases to controls or when data were analyzed.

McConnochie and Roghmann (1986a) compared 53 infants drawn from the patient population of a group practice in Rochester, New York, who had physician-diagnosed bronchiolitis before age 2 years, with 106 controls from the same practice who did not have lower respiratory illnesses during the first 2 years of life and who were matched with cases for sex and age. Parental interviews were conducted when the child had a mean age of 8.4 years. Parents were asked about family history of respiratory conditions and allergy, socioeconomic status, passive smoking, home cooking fuel, home heating methods, and household pets. Passive smoking was defined as current and former smoking of "at least 20 packs of cigarettes or 12 ounces of tobacco while living in the home with the subject." Current and former smoking was scored equally, based on the assumption that the report of either reflected passive smoking in the first 2 years of life. Frequency of paternal smoking was not increased among children who had bronchiolitis. Cases were 2.4 times (95% C.I. = 1.2, 4.8) as likely to have smoking mothers as were controls. The association was stronger in families with older siblings (OR = 8.9); however, a multiplicative test for this interaction did not reach statistical significance. The authors studied 63% of eligible cases and 34% of eligible controls. Although the reasons for exclusion from both groups are detailed, selection bias cannot be excluded completely, and the authors give no information about maternal smoking habits among excluded subjects. Also, overreporting of smoking by parents who were aware of their child's history of bronchiolitis may have introduced biases due to differential misclassification. However, the results were consistent across groups classified according to family history of asthma or allergy, social status, presence of older siblings, and crowding.

Ogston and coworkers (1987) conducted a prospective study of 1,565 infants of primigravidae enrolled antenatally in the Tayside Morbidity and Mortality Study in New Zealand. Information on the father's smoking habits and on the mother's smoking habits during pregnancy was obtained at the first antenatal interview and from a postnatal questionnaire. A summary record was completed when the child was 1 year of age and included a report of the child's respiratory illnesses (defined as "infections of the upper or lower respiratory tract") during the first year of life derived from observations made by health visitors during scheduled visits to see the child. The authors used a multiple logistic regression to control for the possible effects of maternal age, feeding practices, heating type, and father's social class on the relationship between parental smoking and child health. Of the 588 children of nonsmokers in this sample, 146 (24.8%) had respiratory illnesses during the first year of life. Paternal smoking was associated with a 43% increase (95% C.I. = 4.7, 96.1) in the risk of having respiratory illnesses in the first year of life, and this was independent of maternal smoking. The risk of having a respiratory illness was 82% higher (95% C.I. = 25.6, 264.4) in infants of smoking mothers than in infants of nonsmoking parents. Smoking by both parents did not increase the risk of having respiratory illnesses beyond the level observed in infants with smoking mothers and nonsmoking fathers. It is difficult to compare this study with other reports on the same issue because the authors could not distinguish between upper and lower respiratory tract illnesses.

Anderson and coworkers (1988) performed a case-control study of 102 infants and young children hospitalized in Atlanta, Georgia, for lower respiratory tract illnesses before age 2 and 199 age- and sex-matched controls. The unadjusted relative odds of having any family member smoking cigarettes were 2.0 times as high ($p < 0.05$) among cases as among controls (confidence interval was not calculable from the reported data). The effect disappeared, however, after controlling for other factors (prematurity, history of allergy in the child, feeding practices, number of persons sleeping in the same room with the child, immunization of the child in the last month) in a multivariable logistic regression analysis. No information is provided in this report about maternal and paternal smoking separately, and the number of cigarettes smoked at home by each family member was not recorded either. Also, almost 30% of all target cases declined participation in the study, and no information was available on smoking habits in the families of these children. No information is given about number of refusals among controls.

Woodward and collaborators (1990) obtained information about the history of acute respiratory illnesses in the previous 12 months on 2,125 children aged 18 months to 3 years whose parents answered a questionnaire mailed to 4,985 eligible families in Adelaide, Australia. A "respiratory score" was calculated from responses to questions regarding 13 different upper and lower respiratory illnesses. A total of 1,218 parents (57%) gave further consent for a home interview. From this total, parents of 258 cases (children whose respiratory score fell in the top 20% of scores) and 231 "controls" (children whose scores were within the bottom 20% of scores) were interviewed at home. When compared with controls, cases were twice as likely to have a mother who smoked during the first year of life (95% C.I. = 1.3, 3.4). This effect was independent of parental history of respiratory illnesses, other smokers in the home, use of group child care, parental occupation, and level of maternal stress and social support. The authors found no differences in the way smokers and nonsmokers perceived or managed acute respiratory illnesses in their children. Based on this finding, they ruled out that such differences could explain their findings. They also reported that feeding practices strongly modified the effect of maternal smoking; among breast-fed infants, cases were 1.8 times as likely to have smoking mothers as were controls (95% C.I. = 1.2, 2.8), whereas among non-breast-fed infants, cases were 11.5 times as likely to have smoking mothers as were controls (95% C.I. = 3.4, 38.5).

Wright and collaborators (1991) studied the relationship between parental smoking and incidence of lower respiratory tract illnesses in the first year of life in a cohort of 847 white non-Hispanic infants from Tucson, Arizona, who were enrolled at birth and followed prospectively. Lower respiratory illnesses were diagnosed by the infants' pediatricians. Maternal and paternal smoking was ascertained by questionnaire. For verification of smoking habits, the researchers measured cotinine in umbilical cord serum of a sample of 133 newborns who were representative of the population as a whole. Cotinine was detectable in umbilical cord sera of all infants whose mothers reported smoking during pregnancy and in 7 of 100 cord specimens of infants whose mothers said they had not smoked during pregnancy. There was a strong relationship between cotinine level at birth and the amount that the mother reported having smoked during pregnancy.

Children whose fathers smoked were no more likely to have a lower respiratory tract illness in the first year of life than were children of nonsmoking fathers (31.3% vs. 32.2%, respectively). The incidence of lower respiratory tract illnesses was 1.5 times higher (95% C.I. = 1.1, 2.2) in infants whose mothers smoked as in infants whose mothers were nonsmokers. This relationship became stronger when mothers who were heavy smokers were separated from light smokers; 45.0% of children born to mothers who smoked more than 20 cigarettes per day had a lower respiratory illness, compared with 32.1% of children whose mothers smoked 1 to 19 cigarettes per day and 30.5% of children of nonsmoking mothers ($p < 0.05$). The authors tried to differentiate the effects of maternal smoking during pregnancy from those of postnatal exposure to ETS but concluded that the amount smoked contributed more to lower respiratory tract illness rates than did the time of exposure. The authors also found that maternal smoking had a significant effect on the incidence of lower respiratory tract illnesses only for the first 6 months of life; the risk of having a first lower respiratory illness between 6 and 12 months was independent of maternal smoking habits. A logistic regression showed that the effect of maternal smoking was independent of parental childhood respiratory troubles, season of birth, day-care use, and room sharing. Feeding practices, maternal education, and child's gender were unrelated to incidence of lower respiratory illnesses in this sample and were not included in the regression. The analysis also showed a significant interaction between maternal smoking and day-care use; the effects of maternal smoking were significant when the child did not use day care (OR = 2.7; 95% C.I. = 1.2, 5.8) but were weaker and did not reach significance among infants who used day care (OR = 1.9; 95% C.I. = 0.9, 4.0). The authors suggested that day-care use may protect against lower respiratory illnesses by reducing exposure to ETS.

Reese et al. (1992) studied urinary cotinine levels in 491 children, aged 1 month to 17 years, on admission to hospital. Children admitted for bronchiolitis had higher urinary cotinine levels than a group of children of similar age admitted for nonrespiratory illnesses ($p < 0.02$). The researchers concluded that there are objective data linking passive smoking to hospital admission for bronchiolitis in infants.

7.3.2. Summary and Discussion on Acute Respiratory Illnesses

Both the literature referenced in the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) and the additional, more recent studies considered in this report provide strong evidence that children who are exposed to ETS in their home environment are at considerably higher risk of having acute lower respiratory tract illnesses than are unexposed children. Increased risk associated with ETS exposure has been found in different locales, using different methodologies, and in both inpatient and outpatient settings. The effects are biologically plausible (see Section 7.2). Several studies also have reported a dose-response relationship between degree of exposure (as measured by number of cigarettes smoked in the household) and risk of acute respiratory illnesses. This also supports the existence of a causal explanation for the association.

The majority of studies found that the effect was stronger among children whose mothers smoked than among those whose fathers smoked. This is further evidence in favor of a causal explanation, because infants are generally in closer and more frequent contact with their mothers. There are now also fairly convincing data showing that the increased incidence of acute respiratory illnesses cannot be attributed exclusively to in utero exposure to maternal smoke. In fact, Chen (1989) and Chen and coworkers (1986, 1988) reported increased risk of acute respiratory illnesses in Chinese children living with smoking fathers and in the total absence of smoking mothers. This effect also could be attributed either to in utero exposure to the father's smoke or to an effect on the father's sperm. This seems unlikely, however, because no such effects of parental smoking during pregnancy have been described in similar studies performed in Western countries. Furthermore, Woodward and coworkers (1990) found that children of smoking mothers were significantly more prone to acute respiratory illnesses even after mothers who smoked during pregnancy were excluded from the analysis. This clearly suggests the existence of direct effects of ETS exposure on the young child's respiratory health that are independent of in utero exposure to tobacco smoke products.

There is also convincing evidence that the risk is inversely correlated with age; infants aged 3 months or less are reported to be 3.3 times more likely to have lower respiratory illnesses if their mothers smoke 20 or more cigarettes per day than are infants of nonsmoking mothers (Wright et al., 1991). Increases in incidence of 50% to 100% (relative risks of 1.5-2.0) have been reported in older infants and young children. The evidence for an effect of ETS is less persuasive for school-age children, although trends go in the same direction as those reported for younger children. This may be due to a decrease in illness frequency, to physiological development of the respiratory tract or immune system with age, or to a decreased contact between mother and child with age.

Reasonable attempts have been made in most studies to adjust for a wide spectrum of possible confounders. The analyses indicate that the effects are independent of race, parental respiratory symptoms, presence of other siblings, socioeconomic status or parental education, crowding, maternal age, child's sex, and source of energy for cooking. One study (Graham et al., 1990) also showed that the effect of ETS exposure on proneness to acute respiratory illnesses in infancy and early childhood was also independent of several indices of maternal stress, lack of maternal social support, and family dysfunction. Other factors, such as breastfeeding, decreased birthweight, and day-care attendance, have been shown to modify the risk.

Some sources of bias may have influenced the results, but it is highly unlikely that they explain the consistent association between acute lower respiratory illness and ETS exposure. With one exception (Wright et al., 1991), all studies relied exclusively on questionnaires or interviews to assess exposure. Although questions tend to be very specific, overreporting or more accurate reporting of smoking habits by parents of affected children is possible, particularly in case-control and retrospective studies. However, such a bias should affect both respiratory and nonrespiratory outcomes, and at least two studies have shown no association between nonrespiratory outcomes and ETS exposure (Chen et al., 1988; Breese-Hall et al., 1984). Selection bias could not be excluded in some case-control studies, but satisfactory efforts were made to avoid this source of bias in most studies.

7.4. PASSIVE SMOKING AND ACUTE AND CHRONIC MIDDLE EAR DISEASES

The Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) reviewed five studies demonstrating an excess of chronic middle ear disease in children exposed to parental cigarette smoke (Table 7-3). Both reports conclude that the data are consistent with increased rates of chronic ear infections and middle ear effusions in children exposed to ETS at home.

Table 7-3. Studies on middle ear diseases referenced in the Surgeon General's report of 1986

Study	No. of subjects	Age of subjects (years)
Said et al. (1978)	3,290	10-20
Iversen et al. (1985)	337	0-7
Kraemer et al. (1983)	76	Young children (unspecified age)
Black (1985)	450	4-9
Pukander et al. (1985)	264	2-3

7.4.1. Recent Studies on Acute and Chronic Middle Ear Diseases

Several recent studies not referenced in the Surgeon General's report or in the NRC report have addressed the relationship between parental smoking and middle ear illnesses in children (Table 7-4).

Fleming and coworkers (1987) examined retrospectively risk factors for the acquisition of infections of the upper respiratory tract in 575 children less than 5 years of age. Information on smoking habits and on upper respiratory tract infections and ear infections in the 2 weeks prior to interview was obtained from the children's guardians. The authors reported a 1.7-fold increase ($p = 0.01$) in the risk of having an upper respiratory illness in children of smoking mothers when compared with children of nonsmoking mothers. This effect was independent of feeding practices, family income, crowding, day-care attendance, number of siblings aged less than 5 years, child's age, and race. The authors calculated that 10% of all upper respiratory illnesses in the population were attributable to maternal smoking, a proportion that was comparable with that attributable to day-care attendance. There was no relationship between maternal smoking and frequency of ear infections in this population sample.

Willatt (1986) studied 93 children who were the entire group of children admitted to a Liverpool hospital for tonsillectomy (considered an index of frequent upper respiratory or ear infections) during a 3-month period and 61 age- and sex-matched controls. The median age was 6.9 years (range 1.8-14.9). Parents were asked about the number of sore throats in the previous 3 months and the smoking habits of all members of the household. There was a significant

Table 7-4. Recent epidemiologic studies of effects of passive smoking on acute and chronic middle ear diseases

Authors	Population studied	ETS exposure assessment	Outcome variable	Results^1	Observations
Willatt (1986)	93 children aged 2-15 yr. admitted to hospital for tonsillectomy; 61 age- and sex-matched controls	Questionnaire answered by parents	Tonsillectomy	OR = 2.1 (1.1, 4.0) of having smoking mothers	Controlling for birthweight, sex, age, feeding practices, social class, crowding, sore throats in other household members
Fleming et al. (1987)	575 children <5 yr.	Questionnaire answered by child's guardian	Upper respiratory illnesses (URI) and infections in previous 2 weeks	OR = 1.7 for URI when mother smoked; no effect on ear infection	Controlling for feeding practices, income, crowding, day care, siblings, sex, race
Tainio et al. (1988)	198 Finnish newborns followed from birth to age 2.3 yr.	Questionnaire to parents	Recurrent otitis media as diagnosed by pediatricians	No effects	No distinction between maternal and paternal smoking; small sample

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Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Reed and Lutz (1988)	24 cases of acute otitis media; 25 controls	Questionnaire to parents	Abnormal tympanometry	OR = 4.9 (1.4, 17.2) of having smokers at home	Small sample; selection bias cannot be ruled out
Hinton (1989)	115 children aged 1-12 yr. admitted for grommet insertion; 36 controls aged 2-11 yr. in Great Britain	Questionnaire to parents	Being admitted for grommet insertion	OR = 2.1 (1.0, 4.5) of having smoking parents	No control for confounders; selection bias not ruled out
Teele et al. (1989)	877 children observed for 1 yr.; 698 observed for 3 yr.; 498 observed for 7 yr. in Boston, Massachusetts	Questionnaire to parents	Acute otitis media; number of days with middle ear effusion	13% more acute otitis during first yr. of life; more days with middle ear effusion ($p<0.009$) only during first yr.; no effects after controlling for confounders	No distinction between paternal and maternal smoking; parents smoking 1 cig./day included among smokers
Corbo et al. (1989)	1,615 children aged 6-13 yr. in Abruzzo, Italy	Questionnaire to parents	Child's snoring as reported by parents	OR = 1.8 (1.1, 3.0) for moderate smokers (1-19 cig./day); OR = 1.9 (1.2, 3.1) for heavy smokers (≥20 cig./day)	No distinction between maternal and paternal smoking

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Table 7-4. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Strachan et al. (1989)	736 children in third elementary class in Edinburgh, Scotland	Salivary cotinine level	Prevalence of middle ear effusion as assessed by tympanogram	OR for doubling salivary cotinine = 1.14 (1.03, 1.27)	One-third of cases of middle ear effusion attributable to passive smoking; controlling for sex, housing tenure, social class, crowding, gas cooking, damp walls
Takasaka (1990)	77 children aged 4-8 yr. with otitis media with effusion; 134 controls matched for age and sex in Sendai, Japan	Questionnaire to parents	See population studied	No effect	Low power
Etzel et al. (1992)	132 children from day-care facility aged <3 yr.	Serum cotinine levels	Otitis media with effusion	Incidence density ratio 1.4 (1.2, 1.6) for exposed children; increases significant for ages ≤2 years only	8% of cases attributable to ETS exposure

[1] 95% confidence intervals in parentheses.

relationship ($p < 0.05$) between number of episodes of sore throat and number of cigarettes smoked by the mother. The effect was independent of birthweight, sex, child's age, feeding practices, social class, crowding, and number of sore throats and tonsillectomies in other household members. The relative odds of having a smoking mother were 2.1 times as high (95% C.I. = 1.1, 4.0) in children about to undergo tonsillectomy as in children not undergoing tonsillectomy.

Tainio and coworkers (1988) followed 198 healthy newborns from birth to 2.3 years of age. The investigators recorded physician-diagnosed recurrent otitis media (defined as more than four episodes of otitis media during the first 2 years or more than four episodes during the second year). Parental smoking was more frequent (55%) among the infants with recurrent otitis media than in the comparison group (33%; $p < 0.05$). The authors comment, however, that "parental smoking was not a risk factor for recurrent otitis media," probably because there was no significant relationship between parental smoking and recurrent otitis media using definitions of the latter that differed from the one described above. No distinction was made in this study between the possible effects of maternal and paternal smoking. In addition, the study sample was probably too small to obtain reliable risk calculations.

Reed and Lutz (1988) studied 24 of 70 eligible children who had been seen in a family practice office for acute otitis media during a period of 4 months and 25 of 70 eligible children who had been seen for other reasons. Forty-five of these children had tympanograms performed and had information on household smoke exposure. Prevalence of an abnormal tympanogram (indicating the presence of middle ear effusion) was higher among children exposed to smokers at home (OR = 4.86, 95% C.I. = 1.4, 17.2). Results were independent of feeding practices, history of upper respiratory illness in the past month, low socioeconomic status, sex, age, and attendance at a day-care center. Only a small fraction of eligible subjects were included in this study, and the possibility of selection bias as an explanation for the reported results cannot be ruled out.

Hinton (1989) compared 115 children aged 1 to 12 years (mean = 5 years) admitted to a British hospital for grommet insertion with 36 children aged 2 to 11 years (mean = 6 years) with normal ears who were taken from an orthoptic clinic. Prevalence of smoking was significantly higher in parents of cases than in parents of controls (OR = 2.1, 95% C.I. = 1.0, 4.5). Potential sources of selection bias or selective misclassification cannot be determined from the data reported by the author. No effort was made to control for possible confounders.

Teele and coworkers (1989) studied consecutively enrolled children being followed in two health centers in Boston from shortly after birth until 7 years of age. Acute otitis media and middle ear effusion were diagnosed by the children's pediatricians. Data were analyzed for 877 children observed for at least 1 year, 698 children observed for at least 3 years, and 498 children observed until 7 years of age. A history of parental smoking was obtained when each child became 2 years old. A parent was considered a smoker if he or she smoked more than one cigarette per day. The child was considered exposed if either parent was a smoker. The authors reported that the incidence of acute otitis media during the first year of life was 13% higher in children of smoking parents when compared with children of nonsmoking parents ($p < 0.05$), but statistical significance was no longer present after controlling for alleged confounders (site of health care, season of birth, birthweight, socioeconomic status, presence and number of siblings, room sharing, feeding practices, and sibling or parental history of ear infection and allergic diseases). Several of these variables may not have been confounders if they were not related to both parental smoking and incidence of acute otitis media. Controlling for risk factors that are not confounders may result in overcorrection. Parental smoking was not associated with an increased risk for acute otitis media during the first 3 years or 7 years of life. Likewise, parental smoking was associated with a significant increase in the number of days with middle ear effusion, but only during the first year of life ($p < 0.009$), and the effect was no longer present after alleged confounders were controlled for. The authors do not provide information on separate risks for maternal and paternal smoking or on the incidence of acute otitis media and middle ear effusion in children of heavy smokers.

Takasaka (1990) performed a case-control study on 201 children aged 4 to 8 in Sendai, Japan. Sixty-seven subjects had otitis media with effusion, and the remaining 134 children were a control group matched to cases by age, sex, and kindergarten class. The investigators found no significant differences in prevalence of exposure to two or more household cigarette smokers between children with and without otitis media with effusion (no information on either odds ratios or C.I.s was given). The power of this study may have been too low to determine risk factors for middle ear effusions reliably.

Corbo and coworkers (1989) examined 1,615 children aged 6 to 13 years who shared a bedroom with siblings or parents in Abruzzo, Italy. Parents were asked if the child snored and the frequency of snoring. Parents were asked about their own smoking habits; they were considered moderate smokers if the summed total for both parents was fewer than 20 cigarettes per day and heavy smokers if the summed total was 20 or more cigarettes per day. Prevalence of habitual snoring in children increased slightly with the amount of cigarettes smoked by parents; children of heavy smokers were 1.9 times as likely to be habitual snorers as children in nonsmoking households (95% C.I. = 1.2, 3.1), whereas children of moderate smokers were 1.8 times as likely to be habitual snorers as children of nonsmoking parents (95% C.I. = 1.1, 3.0). Habitual snorers were more likely to have had a tonsillectomy, but only if their parents smoked. The authors suggested that these results are plausible because adult smokers are also at increased risk of being habitual snorers.

Strachan and collaborators (1989) performed tympanograms and collected saliva for cotinine determinations in 736 children in the third primary class (ages 6½ to 7½ years) in Edinburgh, Scotland. Median of salivary cotinine concentrations was 0.19 ng/mL for 405 subjects living with no smoker, 1.8 ng/mL for 241 subjects living with one smoker, and 4.4 ng/mL for 124 subjects living with two or more smokers. For a given number of smokers in the household, girls had higher cotinine levels than boys, and children living in rented houses (i.e., of lower socioeconomic level) had higher cotinine levels than children living in houses owned by their parents. The authors found a linear relation between the logarithm of the salivary cotinine concentration and the prevalence of middle ear effusion. The authors calculated odds ratios for abnormal tympanometry relative to children with undetectable cotinine concentrations, after adjustment for sex, housing tenure (rented or owned), social class, crowding, gas cooking, and the presence of damp walls. The odds ratio for a doubling of salivary cotinine concentration was 1.14 (95% C.I. = 1.03, 1.27). At a salivary cotinine concentration of 1 ng/mL, the odds ratio of having an abnormal tympanogram was 1.7, whereas an odds ratio of 2.3 was calculated for a cotinine level of 5 ng/mL. At least one-third of all cases of middle ear effusion may have been attributable to passive smoking.

Etzel and coworkers (1992) studied 132 children who attended a day-care facility during the first 3 years of life. The investigators measured serum cotinine levels and considered a level of 2.5 ng/mL or more to be indicative of exposure to tobacco smoke. The 87 children with serum cotinine above this level had a significantly (38%) higher rate of new episodes of otitis media with effusion during the first 3 years of life than the 45 children with lower or undetectable levels (incidence density ratio = 1.4, 95% C.I. = 1.2, 1.6). The authors calculated that 8% of the cases of otitis media with effusion occurring in this population were attributable to exposure to tobacco smoke.

7.4.2. Summary and Discussion of Middle Ear Diseases

There is some evidence suggesting that the incidence of acute upper respiratory tract illnesses and acute middle ear infections may be more common in children exposed to ETS. However, several studies have failed to find any effect. In addition, the possible role of confounding factors, the lack of studies showing clear dose-response relationships, and the absence of a plausible biological mechanism preclude more definitive conclusions.

Available data provide good evidence demonstrating a significant increase in the prevalence of middle ear effusion in children exposed to ETS. Several studies in which no significant association was found between ETS exposure and middle ear effusion were not specifically designed to test this relationship, and, therefore, either power was insufficient or assessment of the degree of exposure was inadequate. Also, Iversen and coworkers (1985), who assessed middle ear effusion objectively, suggested that the risk associated with passive smoking increased with age. This may explain the negative results of several studies based on preschool children; the sample sizes of these studies may have been inadequate to test for increased risks of 50% or less, as would be expected in children under 6 years of age. The finding of a log-linear dose-response relationship between salivary cotinine levels and the prevalence of abnormal tympanometry in one study (Strachan et al., 1989) adds to the evidence favoring a causal link. Although not all studies adjusted for possible confounders and selection bias cannot be excluded in the case-control studies reviewed, the evidence as a whole suggests that the association is not likely to be due to chance, bias, or factors related to both ETS exposure and middle ear effusion.

The biological mechanisms explaining the association between ETS exposure and middle ear effusion require further elucidation. Otitis media with effusion is usually attributed to a loss of patency of the eustachian tube, which may be enhanced by upper respiratory infection, impaired mucociliary function, or anatomic factors (Strachan et al., 1989). It is possible that pharyngeal narrowing by adenoidal tissue (and, consequently, eustachian tube dysfunction) may be more common in these children. This is suggested by reports of a higher prevalence of maternal smoking among children about to undergo or who have undergone tonsillectomy and by an increased prevalence of habitual snoring among children of smoking parents. Impaired mucociliary clearance has been demonstrated convincingly in smoking adults (U.S. DHHS, 1984). No data are available on mucociliary transport in children exposed to ETS. However, ETS may affect mucociliary clearance in children as in adults. If this were the case and if normal mucociliary clearance is required for rapid resolution of otitis media, exposure to ETS could result in increased prevalence of chronic middle ear effusion.

The increased prevalence of middle ear effusion attributable to ETS exposure has very important public health consequences. Middle ear effusion is the most common reason for hospitalization of young children for an operation and thus imposes a heavy financial burden to the health care system (Black, 1984). There is also evidence suggesting that hearing loss associated with middle ear effusion may have long-term consequences on linguistic and cognitive development (Maran and Wilson, 1986).

7.5. EFFECT OF PASSIVE SMOKING ON COUGH, PHLEGM, AND WHEEZING

Studies addressing the effects of passive smoking on frequency of chronic cough, phlegm, and wheezing were reviewed both in the Surgeon General's report (U.S. DHHS, 1986) and in the report by the NRC (1986) (see Table 7-5).

The Surgeon General's report concluded that children whose parents smoke were found to have 30% to 80% excess prevalence of chronic cough or phlegm compared with children of nonsmoking parents. For wheezing, the increase in risk varied from none to over sixfold among the studies reviewed. The report noted that the association with parental smoking was not statistically significant for all symptoms in all studies, but added that the majority of studies showed an increase in symptom prevalence with an increase in the number of smoking household members in the home. The report stated that the results of some studies could have been confounded by the child's own smoking habits, but noted that many studies showed a positive association between parental smoking and symptoms in children at ages before significant experimentation with cigarettes is prevalent. The report concluded that "chronic cough and phlegm are more frequent in children whose parents smoke compared to nonsmokers. The implications of chronic respiratory symptoms for respiratory health as an adult are unknown and deserve further study" (page 107).

The NRC report concluded that "children of parents who smoke compared with children of parents who do not smoke show increased prevalence of respiratory symptoms, usually cough sputum and wheezing. The odds ratios for the larger studies, adjusted for the presence of parental symptoms, were 1.2-1.8, depending on the symptoms. These findings imply that ETS exposures cause respiratory symptoms in some children" (page 216).

7.5.1. Recent Studies on the Effect of Passive Smoking on Cough, Phlegm, and Wheezing

Several recent studies not considered either in the NRC report (1986) or in the Surgeon General's report (U.S. DHHS, 1986) have addressed the relationship between passive smoking and respiratory symptoms in children (Table 7-6).

McConnochie and Roghmann (1986b) studied 223 of 276 eligible children aged 6 to 10 years without a history of bronchiolitis who were drawn from the patient population of a group practice in Rochester, New York. Information regarding the child's history of wheezing in the previous 2 years, socioeconomic status, family history of respiratory illnesses, and smoking in the household was obtained by questionnaire. Information on breastfeeding was obtained by record checks and interviews. Children whose mothers smoked were more likely to be current wheezers than were children whose mothers did not smoke (OR = 2.2, 95% C.I. = 1.0, 4.8). Neither paternal

Table 7-5. Studies on chronic respiratory symptoms referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Respiratory symptoms	Surgeon General	NRC
Bland et al. (1978)	3,105	Children/adol. (12-13)	Cough	X	X
Charlton (1984)	15,000	Children/adol. (8-19)	Cough	X	
Colley et al. (1974)	2,426	Children (6-14)	Cough	X	X
Dodge (1982)	628	Children (8-10)	Wheeze, phlegm, cough	X	X
Ekwo et al. (1983)	1,355	Children (6-12)	Cough, wheeze	X	
Kasuga et al. (1979)	1,937	Children (6-11)	Wheeze, asthma	X	
Lebowitz and Burrows (1976)	1,525	Children (<15)	Cough, phlegm, wheeze	X	X
Schenker et al. (1983)	4,071	Children (5-14)	Cough, phlegm, wheeze	X	X
Schilling et al. (1977)	816	Children/adol. (7-16)	Cough, phlegm, wheeze	X	X
Tager et al. (1979)	444	Children/adol. (5-19)	Cough, wheeze		X
Ware et al. (1984)	10,106	Children (6-13)	Cough, wheeze, phlegm		X
Weiss et al. (1980)	650	Children (5-9)	Cough, phlegm, wheeze	X	X

Table 7-6. Recent epidemiologic studies of effects of passive smoking on cough, phlegm, and wheezing

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
McConnochie and Roghmann (1986b)	223 children aged 6 to 10 yr. in Rochester, New York	Parental questionnaire	Wheezing in the previous 2 yr.	OR = 2.2 (1.0, 4.8) for maternal smoking; no effect of paternal smoking	Effect disappeared after controlling for confounders; strong interaction between smoking and family history of allergy (OR = 4.5 [1.7, 12.0])
Park and Kim (1986)	3,651 children aged 0 to 14 yr. in South Korea	Questionnaire to household members	Cough in the 3 mo. prior to interview	OR = 2.4 (1.4, 4.3) for families smoking 1 to 14 cig./day; OR = 3.2 (1.9, 5.5) for families smoking ≥15 cig./day	Results only significant among families whose adult members did not have chronic cough

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Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Bisgaard et al. (1987)	5,953 infants enrolled at birth in Denmark	Maternal questionnaire	Episodes of wheeze during first yr. of life	OR = 2.7 (1.8, 4.0) for children whose mothers smoked ≥3 cig./day	Controlling for social status and sex; almost one-third of original sample did not participate in the study
Geller-Bernstein et al. (1987)	80 children aged 6 to 24 mo. in Israel	Parental questionnaire	Persistent wheeze as assessed by physician after 1½ yr. of followup	OR = 3.1 (1.1, 8.9) for having smoking parents	No control for parental symptoms
Cogswell et al. (1987)	100 infants of allergic parents enrolled at birth; 73 still followed at age 5 yr.	Parental questionnaire	Number of subjects who developed wheezing at different times after birth	By 5 yr., 63% of parents who smoked had wheezing children, compared with 37% of nonsmoking parents ($p<0.05$)	> one-fourth of subjects lost to followup
Toyoshima et al. (1987)	48 wheezy children <3 yr. followed in Osaka, Japan	Parental questionnaire	Number of children still wheezing at end of followup	OR = 11.8 (1.3, 105.0) for children living in smoking households	Selection bias cannot be ruled out
Tsimoyianis et al. (1987)	193 12- to 17-year-old high school athletes	Questionnaire to the child on household smoking habits	Self-report of cough, bronchitis, wheeze, and shortness of breath	No effect on bronchitis, wheeze, shortness of breath. Increased frequency of cough ($p=0.08$)	Reporting bias cannot be ruled out

(continued on the following page)

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Andrae et al. (1988)	4,990 children aged 6 mo. to 16 yr. in Norrkoping, Sweden	Self-report of smoking by parents	Exercise-induced cough as reported by parents	OR = 1.4 (1.1, 1.8) for children whose parents smoked	No effort made to control for active smoking in older children
Somerville et al. (1988)	7,144 children aged 5 to 11 yr. in England and Scotland; 134 controls matched for age and sex in Sendai, Japan	Questionnaire answered by child's mother	Parental reports of respiratory symptoms in the child	Among English children whose parents smoked ≥20 cig./day OR = 1.6 (1.2, 2.2) of having "wheezy chest most nights"	
Rylander et al. (1988)	67 children aged 4 to 7 yr. hospitalized with respiratory syncytial virus bronchiolitis in Stockholm, Sweden	Parental questionnaire	Subsequent occasional and recurrent wheezing	Occasional wheezing OR = 4.3 (1.1, 16.4) in children of smoking parents; no effect on recurrent wheezing	Small number of subjects
Strachan (1988)	1,012 schoolchildren 6.5 to 7.5 yr. old in Edinburgh, Scotland	Parental questionnaire	Respiratory symptoms in children	No effect on wheeze; cough at night, OR = 1.6 (1.1, 2.6) in children living with one smoker; OR = 2.5 in children living with two smokers	

(continued on the following page)

Table 7-6. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Lewis et al. (1989)	60 cases of chronic cough aged <6 yr.; 60 controls; in Salford, United Kingdom	Parental questionnaire	See population studied	OR = 1.7 (0.8, 3.5) in children living with a smoker	Low power
Neuspiel et al. (1989)	9,670 children enrolled at birth in Great Britain	Parental questionnaire at birth, at age 5 yr. and at age 10 yr.	Wheeze between ages 1 and 10 yr.	Cumulative incidence: 5.2% mother non-smoker, 6.6% mother smoked 1 to 4 cig./day, 7.5% mother smoked 5 to 11 cig./day, 8.1% mother smoked 15 to 24 cig./day, 8.9% mother smoked >24 cig./day	Independent of sex, allergy, smoking during pregnancy, paternal smoking, crowding, dampness, feeding practices, gas cooking, social status, and maternal respiratory symptoms
Chan et al. (1989a)	134 children 7 yr. of age in London, England, <2,000 g birthweight; 123 controls with normal birthweight	Parental questionnaire	Wheeze and cough	OR = 2.7 (1.3, 5.5) of having wheeze at age 7 in children of smoking mothers, OR = 2.4 (1.3, 4.6) of having cough	Effects on wheeze independent of confounders; effects on cough disappeared after controlling for confounders

[1] 95% confidence intervals in parentheses.

smoking nor total household smoking had any influence on the prevalence of wheezing. When the authors controlled for family history of respiratory allergy, direct effects of maternal smoking on prevalence of wheezing failed to reach statistical significance. However, there was a strong association between maternal smoking and wheezing among children with a positive family history of respiratory allergy (OR = 4.5, 95% C.I. = 1.7, 12.0), and the interaction between these terms was highly significant in multivariable analysis, suggesting the combined importance of both genetic factors and maternal smoking.

Park and Kim (1986) studied 3,651 children aged 0 to 14 from a randomized, clustered sample of households in South Korea (response rate: 89%). A questionnaire was administered to household members about their smoking habits and respiratory symptoms. Mothers answered questions about the presence of cough in the child in the 3 months prior to interview. The authors reported dose-response relationships between the child's cough and number of smokers in the family, number of smokers in the same room, number of cigarettes smoked by all family members, and number of cigarettes smoked by parents. The relationship was present in children of different ages (less than 5 years, 6 to 11 years, and 12 to 14 years). The authors controlled for parental education, socioeconomic status, birth rank, parental age, birth interval, number of family members, and number of siblings. Family members with cough or with morning phlegm production were significantly more likely to live with children with cough. After correcting for these two factors, chronic cough was 2.4 times as likely in children of families whose members smoked 1 to 14 cigarettes per day (95% C.I. = 1.4, 4.3) and 3.2 times as likely in children of families whose members smoked more than 15 cigarettes per day (95% C.I. = 1.9, 5.5). However, effects were more noticeable and only reached statistical significance in children of families whose adult members did not have chronic cough.

Bisgaard and coworkers (1987) studied 5,953 infants of a total of 8,423 eligible newborns (71%) enrolled in a prospective study. At the age of 1 year, the child's mother was interviewed regarding episodes of wheeze during the previous year and possible risk factors for wheezing. The risk of wheezing was 2.7 times as high (95% C.I. = 1.8, 4.0) in children whose mothers smoked three or more cigarettes per day as in children whose mothers smoked fewer than three cigarettes per day. Results were independent of social status and sex of the child. The authors decided not to control for quarter of birth or use of day-care facilities, with the assumption that these factors did not modify the relationship between maternal smoking and wheezing. Also, biases could have been introduced by the fact that almost one-third of the original sample was not included in the analysis.

Geller-Bernstein and coworkers (1987) studied 80 children aged 6 to 24 months who had been seen as outpatients or inpatients in Israel for wheezing and who had a diagnosis of atopy.

The children were examined every 6 months during 4 years by a physician. At the end of assessment, the authors classified children as having "recovered" if they had been symptom-free for at least 1 (the last) year; otherwise they were classified as "persistent wheezers." "Persistent wheezers" were more likely to have smoking parents than were "recovered" children (OR = 3.1, 95% C.I. = 1.1, 8.9). This result was independent of changes in IgE levels during the study period. The authors did not control for the possible confounding effect of parental symptoms.

Cogswell and coworkers (1987) studied 100 newborns who had at least one parent with a history of hay fever or asthma. Ninety-two children were still being followed at 1 year of age and 73 at the age of 5 years. Children were examined periodically and whenever they had signs of respiratory illness. At the child's first birthday, the number of those who had developed wheezing was equally distributed between parents who did or did not smoke. By the age of 5 years, however, 62% of parents who smoked had children who had wheezed compared with 37% in nonsmoking families ($p < 0.05$). It is unlikely that these results can be explained by the confounding effect of parental symptoms, because all parents were allergic by definition. It is also quite unlikely that preferential withdrawal of nonwheezing children of smoking parents could have biased the results.

Toyoshima and coworkers (1987) from Osaka, Japan, followed 48 of 65 wheezy infants and children less than 3 years old for up to 4 years. Outcome information was obtained from charts or by telephoning the child's mother. Among 18 children who were still symptomatic 25 to 44 months after their first visit, 17 lived with smokers compared with 13 of 22 children who lived with smokers and who stopped having symptoms during followup (OR = 11.8, 95% C.I. = 1.3, 105.0). Results were independent of family history of allergy, feeding practices, and disturbances at birth. Selection bias related to the number of subjects lost for followup or with missing information could have influenced the results of this study.

Tsimoyianis and collaborators (1987) evaluated the effects of exposure to ETS on respiratory symptoms in a group of 12- to 17-year-old high school athletes (N = 193). Histories of smoking by all household members were obtained for all subjects. Athletes exposed to ETS at home were more likely to report cough than were unexposed athletes ($p = 0.08$). Frequency of bronchitis, wheeze, and shortness of breath was similar in both groups. A greater awareness of the smoking habits of those around them by subjects with cough cannot be excluded as an explanation of these findings, but this source of bias cannot explain the exposure-response trends for ETS and lung function seen in this same sample (see Section 7.8.1).

Andrae and collaborators (1988) mailed questionnaires to the parents of 5,301 children aged 6 months to 16 years living in the city of Norrkoping, Sweden. Data were obtained from 4,990 children (94% response rate). Children with parents who smoked had exercise-induced cough more often than did children of nonsmokers (OR = 1.4, 95% C.I. = 1.1, 1.8). Exposure to ETS interacted with living in houses with damage by dampness; children exposed to both had more exercise-induced cough and allergic asthma when compared to those exposed to only one or neither. Results of this cross-sectional study may have been biased by preferential reporting of symptoms by smoking parents, although a reliability study performed in a random sample was reported to confirm 95% of the answers regarding respiratory symptomatology. In addition, no effort was made to control for active smoking in older children.

Somerville and coworkers (1988) enrolled 88% of 8,118 eligible children aged 5 to 11 from England and Scotland. Data on the child's respiratory symptoms and parental smoking were obtained from a self-administered questionnaire completed by the child's mother. After exclusions for missing data, the proportions of children available ranged from 60.9% to 63.9% of all subjects, depending on the variables involved. Logistic regression analysis was used to control for child's age, presence of siblings, one- or two-parent families, paternal employment, social class, maternal smoking during pregnancy, overcrowding, maternal education, maternal age, triceps skinfold thickness, and birthweight. For Scottish children (who were only 19% of all subjects), the authors found a significant relationship between number of cigarettes smoked at home and "chest ever wheezy" ($p < 0.01$; OR not reported). Among English children, there was a significant relationship between number of cigarettes smoked at home by mother and father together and prevalence of a wheezy or whistling chest most nights (adjusted OR in children whose parents smoked 20 cig./day = 1.6; 95% C.I. = 1.2, 2.2). Attacks of bronchitis and cough during the day or at night were also significantly correlated with number of cigarettes smoked by parents in the English sample; odds ratios in children of parents who smoked 20 cigarettes per day were 1.4 and 1.3, respectively, but no confidence intervals were reported. The authors concluded that the effect of parental smoking on respiratory symptoms in this age group is small and requires a large number of subjects to be detected.

Rylander and collaborators (1988) from Stockholm, Sweden, studied 67 children aged 4 to 7 years who had been hospitalized with virologically proven RSV infections before age 3. Questionnaires were mailed to parents regarding their smoking habits and the child's history of wheezing illnesses after the initial episode. Children who had subsequent occasional wheezing (N = 21) were more likely to have smoking parents than those (N = 24) who had no subsequent respiratory symptoms (OR = 4.3, 95% C.I. = 1.1, 16.4). However, frequency of parental smoking among children who had no subsequent respiratory symptoms was not significantly different from that of children who had subsequent recurrent wheezing. The inconsistency of the results in this study may be explained by the small number of subjects involved.

Strachan (1988) studied 1,012 of a target sample of 1,095 schoolchildren aged 6.5 to 7.5 years in Edinburgh, Scotland. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. There was no relationship between number of smokers in the household and prevalence of wheezing in the population. Cough at night (> 3 nights in the past month) was more likely to occur in children living with one smoker (OR = 1.6; 95% C.I. = 1.1, 2.6) or two smokers (OR = 2.5; 95% C.I. = 1.5, 4.0) than in children living with nonsmokers. Occurrence of "chesty colds" in children was also more frequent in households with one (OR = 1.3; 95% C.I. = 0.9, 1.9) or two smokers (OR = 1.9; 95% C.I. = 1.3, 3.0).

A subsequent report (Strachan et al., 1990) based on the same population sample studied the relationship between salivary cotinine levels and respiratory symptomatology in a subset of 770 children (see also Strachan et al. [1989], Section 7.4.1). The authors found no relationship between cotinine levels and wheezing or frequent night cough. Frequency of chesty colds was significantly correlated with quintals of salivary cotinine ($p < 0.01$). The authors noted that objective markers of recent exposure to ETS may not adequately reflect exposure at some critical period in the past. They also noted that there may be different ways of understanding the concept of "wheezing" and proposed that this could explain the lack of association between this symptom and both questionnaire-based and cotinine-based assessment of exposure to ETS in their sample.

Lewis and coworkers (1989) performed a case-control study of risk factors for chronic cough in children under 6 years in Salford, United Kingdom. They enrolled 60 children referred to a pediatric outpatient clinic with cough lasting more than 2 months or frequent episodes of cough without wheeze. These 60 subjects were compared with controls admitted for routine surgical procedures. Children with chronic cough were 1.7 times (95% C.I. = 0.8, 3.5) as likely to live with a smoker as were controls. Because of the small number of subjects and the high prevalence of parental smoking (> 50%), the power of this study may have been too low to allow for meaningful conclusions.

Neuspiel and coworkers (1989) studied 9,670 of 9,953 eligible children enrolled at birth in Great Britain. Information on parental smoking was obtained at birth, at age 5 years, and at age 10 years. Outcome data were obtained from maternal interviews when the children were 10 years old. Children of smoking mothers had 11% higher risk (95% C.I. = 2%, 21%) of wheezing between ages 1 and 10 than did children of nonsmoking mothers. An exposure-response relationship was also present: Cumulative incidence was 5.2% in children whose mothers were nonsmokers, 6.6% in children whose mothers smoked 1 to 4 cigarettes per day, 7.5% in children whose mothers smoked 5 to 14 cigarettes per day, 8.1% in children whose mothers smoked 15 to 24 cigarettes per day, and 8.9% in children whose mothers smoked more than 24 cigarettes per day. The risk also was increased in children of mothers who did not smoke during pregnancy but were smokers thereafter (RR = 2.2, 95% C.I. = 1.2, 3.9). The association persisted after a logistic regression model was used to control for the effect of child's sex, child allergy, paternal smoking, parental allergy, crowding, bedroom dampness, feeding practices, gas cooking, and social status. The increase in risk was cut approximately in half but did not disappear when additional corrections for maternal respiratory symptoms and for a measure of maternal depression were made. Results of this study may be explained in part by preferential reporting of wheezy illnesses by smoking mothers. However, it is unlikely that the association between maternal smoking and wheezy illnesses found in this study can be explained exclusively by uncontrolled sources of bias; there was a striking exposure-response effect, and the association persisted after controlling for most known confounders and was independent of maternal smoking during pregnancy.

Chan and collaborators (1989a) studied 134 children aged 7 years out of 216 eligible infants of under 2,000 g birthweight who were admitted to the neonatal unit of two hospitals in London, England. Parents of these 134 children and of 123 control schoolchildren born in the same period but with normal birthweight completed a self-administered questionnaire on respiratory illnesses and on social and family history. At age 7, children whose mothers smoked were at increased risk of having frequent wheeze independent of their neonatal history (adjusted OR = 2.7; 95% C.I. = 1.3, 5.5), although the increase only reached statistical significance for children of normal birthweight. Prevalence of frequent cough was also more likely to occur in children of smoking mothers (OR = 2.4, 95% C.I. = 1.3, 4.6), and the association was significant for both cases and controls studied separately. The authors performed a logistic regression to control for possible confounders (only the low-birthweight group was included). The relationship between frequent wheeze and maternal smoking persisted among low-birthweight children after controlling for family history of asthma, atopy, socioeconomic status, and use of neonatal oxygen. The relationship between frequent cough and maternal smoking was no longer significant among low-birthweight infants after controlling for the same possible confounders. For the low-birthweight group, the authors assessed the reliability of some of the responses to their questionnaires; there was a high correlation (r = 0.96) between the number of hospitalizations reported by parents and those documented in the outpatient clinic of the neonatal unit that followed the infants. The authors concluded that misclassification due to parental failure to recall previous respiratory illnesses in the low-birthweight group was unlikely.

Krzyzanowski and collaborators (1990) studied a sample of 298 children aged 5 to 15 who were family members of county employees enrolled in a prospective study. Parents answered a questionnaire on their smoking habits and on respiratory symptoms in their children. Indoor formaldehyde concentrations in the living environment also were measured. Prevalence rates of chronic bronchitis (as diagnosed by a physician) were significantly higher in children exposed both to ETS and to formaldehyde concentrations of over 60 parts per billion than in children with one or none of these exposures. The authors also reported that similar effects were not seen in adults.

Dijkstra and collaborators (1990) obtained consent for participation in their study for 1,051 of a total of 1,314 (80%) eligible 6- to 12-year-old schoolchildren from a rural area in The Netherlands. Parents completed a self-administered questionnaire on their smoking habits and on respiratory symptoms in their children. Complete information was available for 775 children. When compared to children of nonsmoking households, children exposed to ETS at home were significantly more likely to have cough on most days for at least 3 months consecutively (OR = 2.5, 95% C.I. = 1.1, 5.6), wheezy or whistling sounds in the chest in the last year (OR = 1.9; 95% C.I. = 1.0, 3.5), and attacks of shortness of breath with wheeze in the last year (OR = 2.0; 95% C.I. = 0.9, 4.2). Exposed children were significantly more likely to have one or more of the above symptoms than were unexposed children (OR = 2.0; 95% C.I. = 1.2, 3.7). Results were still significant after adjusting for parental respiratory symptoms and for maternal smoking during pregnancy. The authors also measured nitrogen dioxide in the homes of all children but found no association of the latter with respiratory symptoms.

Mertsola and coworkers (1991) followed prospectively for 3 months 54 patients aged 1 to 6 years from Turku, Finland, who had a history of recurrent attacks of wheezy bronchitis. The parents were told to record the symptoms of the child daily and were asked to bring their child to the hospital emergency room if the child developed signs of an acute respiratory infection. Incidence of prolonged wheezing episodes (> 4 days) during followup was significantly more likely in children exposed to ETS than in unexposed children (OR = 4.8; 95% C.I. = 1.9, 12.6). The result was independent of number of siblings, age, sex, medication, and personal history of allergy.

7.5.2. Summary and Discussion on Cough, Phlegm, and Wheezing

Recent studies reviewed in this report that were not included either in the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986) substantially confirm the conclusions reached in those two reports. There is sufficient evidence for the conclusion that ETS exposure at home is causally associated with respiratory symptoms such as cough, phlegm, or wheezing in children.

The evidence is particularly strong for infants and preschool children; in this age range, most studies have found a significant association between exposure to ETS (and especially to maternal smoking) and respiratory symptoms in the children, with odds ratios generally ranging between 1.2 and 2.4. Selection bias may have influenced the results of certain cross-sectional studies; retrospective studies also may have been biased by preferential recall of their children's symptoms by smoking parents. However, the presence of a causal relationship is strongly supported by the consistency of the results for different geographic areas (Japan, Korea, People's Republic of China, Europe, and North America) and by the positive findings in prospective studies that are less subject to selection and recall biases.

In addition, efforts have been made by all researchers to control for possible confounders and to avoid sources of bias. It is not feasible for each study to take into account all possible factors that may affect the relationship under study; some of these factors may even be unknown at present. However, all reviewed studies have controlled for at least some of the best-known confounders (family history of respiratory illnesses, parental respiratory symptoms, socioeconomic status, crowding, presence of other siblings, home dampness, gas cooking, maternal level of education, perinatal problems, low birthweight, maternal age, birth rank, and maternal stress, or depression). Of these possible confounders, a history of respiratory symptoms in parents has been particularly scrutinized. The NRC report (1986) noted that bias may be introduced by parents who have a history of respiratory illnesses for several reasons. These parents may overstate their children's symptoms, or their children actually may have more respiratory illnesses and symptoms. The latter possibility could be the result of intrafamily correlation of susceptibility (referred to as familial resemblance by Kauffmann and coworkers [1989a]). Because smokers are more likely to have respiratory symptoms, one would expect that controlling for respiratory symptoms in parents would result in a decrease in statistical significance of the relationship between ETS and symptoms in the child. In fact, most recent studies that have addressed the issue report that controlling for family history of respiratory symptoms decreases but does not entirely explain the increased risk of respiratory symptoms in young children exposed to ETS. It has been stressed, however, that the use of these statistical adjustment procedures may induce an underestimation of the effect of passive smoking; this would indeed be the case if parents with symptoms (and thus more likely to be smokers) were more prone to report symptoms in their children than were parents without symptoms. Several studies also have found that the effect is independent of maternal smoking during pregnancy and cannot be attributed exclusively to intrauterine exposure to tobacco products (although the latter may potentiate the effects of postnatal exposure to ETS).

The evidence is significant but less compelling for a relationship between exposure to ETS and respiratory symptoms in school-age children. Odds ratios for this age group are usually between 1.1 and 2.0. Several studies have shown that, among school-age children, there are significant differences in susceptibility to ETS exposure between individuals. There is, in fact, evidence showing that several factors may amplify the effects of passive smoking: prematurity, a family history of allergy, a personal history of respiratory illnesses in early childhood, and being exposed to other environmental pollutants such as formaldehyde. In addition, long-term exposure may have more important effects than short-term exposure. One study of 7-year-old children (Strachan, 1988; Strachan et al., 1990) used both questionnaires regarding smoking habits in the household and the child's saliva cotinine levels as indices of exposure to ETS. The authors found a significant increase in the risk of having frequent cough when the questionnaire was used to ascertain exposure, but no association between saliva cotinine levels and frequency of cough. As the authors remarked, biochemical markers permit characterization of recent tobacco smoke exposures, but they may not adequately reflect exposure at some critical period in the past. Recent studies of intraindividual variability of cotinine levels also have suggested that it may be misleading to assess the validity of questionnaire measures against a single determination of a biologic marker (Coultas, 1990b; Idle, 1990). It is thus possible that associations evaluated with salivary cotinine are likely to underestimate the true relationship between passive smoking and respiratory morbidity (Strachan et al., 1990).

In the case of older children who may have started experimenting with cigarettes, the confounding effects of active smoking need to be considered. Most researchers have been aware of this problem and have attempted to control for it. A great difficulty lies in misclassification of smokers due to underreporting. Young persons may be reluctant to admit smoking cigarettes. Data are often obtained from parents, who may not be aware of the child's smoking.

In summary, this report concludes that ETS exposure at home causes increased prevalence of respiratory symptoms in infants and young children. There is also good evidence indicating that passive smoking causes respiratory symptoms in some older children, particularly in children who have predisposing factors that make them more susceptible to the effects of ETS.

7.6. EFFECT OF PASSIVE SMOKING ON ASTHMA

Studies addressing the effects of passive smoking on frequency of asthma were directly reviewed only in the Surgeon General's report (U.S. DHHS, 1986) and not explicitly in the report on environmental tobacco smoke by the NRC (1986). The Surgeon General's report concluded that epidemiologic studies of children had shown no consistent relationship between the report of a doctor's diagnosis of asthma and exposure to involuntary smoking. The report pointed out that, although one study had shown an association between involuntary smoking and asthma (Gortmaker et al., 1982), others had not (Schenker et al., 1983; Horwood et al., 1985). This variability was attributed to differing ages of the children studied, differing exposures, or uncontrolled bias. The report also concluded that maternal cigarette smoking may influence the severity of asthma. Alteration of nonspecific bronchial responsiveness was proposed as a mechanism for this latter effect.

7.6.1. Recent Studies on the Effect of Passive Smoking on Asthma in Children

Several new cross-sectional and longitudinal studies published after the U.S. Surgeon General's report (U.S. DHHS, 1986) was released have addressed the relationship between frequency, incidence, and severity of asthma and parental cigarette smoke (Table 7-7). (Studies on the relationship between ETS exposure and bronchial responsiveness were reviewed in Section 7.2.4.)

Burchfield and coworkers (1986) studied 3,482 nonsmoking children and adolescents ages 0 to 19 years out of 4,378 eligible subjects from Tecumseh, Michigan. Subjects or their parents (for children aged 15 years or younger) answered questionnaires on past history of asthma and other respiratory conditions. Information on parental smoking habits was obtained from each parent. Prevalence rates of asthma were higher among children whose parents both had smoked during the child's lifetime than among children whose parents had never smoked. The effect was stronger and only reached statistical significance for males (OR for boys = 1.7, 95% C.I. = 1.2, 2.5 in boys; OR for girls = 1.2, 95% C.I. = 0.8, 1.9). Children with one parental smoker were not more likely to have asthma than was the unexposed reference group. When results were stratified by parental history of respiratory conditions, there was some reduction in the magnitude of the parental smoking effects, but results remained significant for asthma in males. Results were also independent of age, parental education, family size, a diagnosis of hay fever, and a history of other allergies. Reporting bias and diagnostic bias may in part explain the relationships reported in this study; smoking parents may be more likely to report asthma in their children, and physicians may be more prone to diagnose asthma in children of smoking parents.

D. Evans and coworkers (1987) studied 191 out of 276 children aged 4 to 17 years from low- income families who were receiving health care for physician-diagnosed asthma in New York. Excluded children were younger and had fewer emergency room visits for asthma than those with complete data. The authors suggested that the latter subjects had more severe asthma than the general community population of low-income children with asthma. Emergency room visits and hospitalizations for asthma were assessed by reviewing hospital records. Passive smoking by the child was measured by asking one parent if he or she or anyone else in the house smoked. Authors did not differentiate between maternal and paternal smoking; no attempt was made to assess the degree of exposure to cigarette smoke. Eight children who were active smokers were excluded. There was a significant correlation between number of emergency room visits and cigarette smoke exposure ($p = 0.008$); the mean frequency (± SD) of annual emergency room visits observed for children exposed to passive smoking was 3.1 ± 0.4, compared with 1.8 ± 0.3 for children from nonsmoking households. Passive smoking had no effect on either the frequency of days with asthma symptoms or on the annual frequency of hospitalizations. Results were

Table 7-7. Recent epidemiologic studies of effects of passive smoking on asthma in childhood

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Burchfield et al. (1986)	3,482 nonsmoking children 0 to 19 yr. in Tecumseh, Michigan	Questionnaire answered by subjects or parents	Prevalence of asthma	OR = 1.7 (1.2, 2.5) for boys; OR = 1.2 (0.8, 1.9) for girls	Independent of parental respiratory illness, age, parental education, family size, and allergies
D. Evans et al. (1987)	191 children aged 4 to 17 yr. in New York, New York	Parental questionnaire	Emergency room visits and hospitalizations for asthma (from medical records)	3.1 ± 0.4 vs. 1.8 ± 0.3 ($p=0.008$) emergency room visits in children of smoking and non-smoking parents	No distinction made between maternal and paternal smoking; independent of race and parental employment status
O'Connor et al. (1987)	292 subjects aged 6 to 21 yr. in Boston, Massachusetts	Parental questionnaire	Bronchial response to cold air	Significantly increased response in asthmatics whose mothers smoked	No increase in nonasthmatics whose mothers smoked

(continued on the following page)

Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Murray and Morrison (1989)	415 children aged 1 to 17 yr. with asthma in Vancouver, Canada	Parental questionnaire	Asthma symptom score for severity of asthma	Higher scores ($p<0.01$) in children of smoking mothers	Stronger effect in boys and older children
Krzyzanowski et al. (1990)	298 children aged 5 to 15 yr. in Tucson, Arizona	Parental questionnaire	Parental reports of asthma in their children	OR = 9.0 (2.4, 34.0) for children exposed to ETS and formaldehyde vs. nonexposed	Small sample
Sherman et al. (1990)	770 children aged 5 to 9 yr. followed for 11 yr. in Boston, Massachusetts	Parental and subject questionnaire	Physician diagnosis of asthma	No effect of parental smoking on prevalence or incidence of asthma	No effort to assess effect of heavy smoking by parents; no control for socioeconomic status
Weitzman et al. (1990)	4,331 children aged 0 to 5 yr. (U.S. National Health Interview Survey)	Maternal questionnaire	Asthma for at least 3 mo. at time of questionnaire	OR = 2.1 (1.3, 3.3) for children whose mothers smoked ≥ 10 cig./day	Independent of race, sex, family size, presence of both parents, and number of rooms

(continued on the following page)

Table 7-7. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Oldigs et al. (1991)	11 asthmatic children	Direct exposure to ETS for 1 hour	Changes in lung function	No effect	No assessment of effect of chronic exposure
Martinez et al. (1992)	774 children aged 0 to 5 yr. followed for several years in Tucson, Arizona	Parental questionnaire	Physician diagnosis of asthma	OR = 2.5 (1.4, 4.6) for children of low maternal education whose mothers smoked ≥10 cig./day	No effect among children of better educated mothers
Ehrlich et al. (1992)	228 children; 72 with acute asthma; 35 with nonacute asthma and 121 controls	Cotinine levels in urine of children; smoking by maternal caregiver	Emergency room and asthma clinic visits	Higher levels of cotinine in asthmatics OR = 1.9 (1.0, 3.4)	Similar cotinine levels in acute and nonacute asthmatics

[1] 95% confidence intervals in parentheses.

independent of ethnicity and parental employment status. The association could have been explained by lower compliance with prescribed treatment of their children's asthma by smoking parents, but the authors found no significant differences in compliance (as assessed by an index of asthma self-management activities) between smoking and nonsmoking parents. The authors estimated that the additional cost for emergency care for asthma was $92 ± $68 per family per year.

O'Connor and coworkers (1987) performed bronchial challenges with subfreezing air in 292 subjects 6 to 21 years of age. They were selected from 879 eligible subjects of the same age who were participating in a longitudinal study on respiratory illnesses in East Boston. An attempt was made to include as many subjects as possible who reported a history of asthma or wheezing on standardized questionnaires. Therefore, the latter group of subjects were overrepresented among those tested. The change in FEV_1 caused by subfreezing air was significantly higher in asthmatic subjects whose mothers smoked at least one cigarette per day than in those whose mothers were nonsmokers. This relationship was independent of age, sex, height, personal smoking, paternal smoking, atopy, and baseline lung function. There was no relationship between maternal smoking and response to cold air among nonasthmatics.

Murray and Morrison (1989) studied 415 nonsmoking children aged 1 to 17 years consecutively referred to an allergy clinic in Vancouver, Canada, for asthma or recurrent wheezing of the chest. Questionnaires were administered to the parents of all children at the time of their first visit. Forced expiratory flows and bronchial reactivity to histamine also were measured. An asthma symptom score was calculated for each subject based on the severity of asthma and the need for medication, as reported by parents. Children of smoking mothers had significantly higher indices of asthma severity ($p < 0.01$) and significantly lower FEV_1 (84.4% predicted vs. 77.3% predicted, $p < 0.01$) than did children of nonsmoking mothers. They were also significantly more responsive to histamine than were children of nonsmoking mothers ($p = 0.01$). The effect was present in both genders but was stronger for boys than for girls. Also, the effect was stronger for older children (12 to 17 years of age) than for children 6 years of age or younger. The authors also reported a positive correlation between length of exposure to ETS and asthma symptom score. It is unlikely that these results can be explained by parental overreporting because the association between passive smoking and severity of symptoms paralleled that between passive smoking and objective measurements of severity.

In their previously reviewed report (Section 7.5.1), Krzyzanowski and coworkers (1990) found that children exposed to ETS and to more than 60 ppb of formaldehyde had significantly higher prevalence rates of asthma than those exposed to only one of these contaminants or to none (OR for the latter comparison = 9.0; 95% C.I. = 2.4, 34.0). No such association was seen among adult household members. It is unlikely that this association is attributable to parental overreporting of asthma because the authors relied on objective measurement of indoor formaldehyde concentrations.

Sherman and collaborators (1990) reported on the results of a longitudinal study of determinants of asthma in a sample of 770 schoolchildren enrolled in East Boston in 1974. Questionnaires were used to obtain data on respiratory symptoms and illnesses, cigarette smoking history of parents and children, and household demographics. They were administered on entry and for 11 consecutive years (1978-1988). Parents answered for children aged 9 or less, except for questions on the child's smoking history. The authors identified risk factors for the onset of asthma, the occurrence of which antedated the time of first diagnosis of asthma. There was no significant relationship between maternal smoking and either prevalence of asthma at the first survey or incidence of new cases of asthma during followup (sex-adjusted RR = 1.1; 95% C.I. = 0.7, 1.7). The authors considered it unlikely that this finding could be due to exposure levels too low to increase the risk of asthma. However, no effort was made to assess the relationship between incidence of asthma and number of cigarettes smoked by parents. Likewise, no effort was made to determine the possible role of factors known to modify exposure to ETS such as parental socioeconomic level (Strachan et al., 1989).

Weitzman and coworkers (1990) studied 4,331 children aged 0 to 5 years who were part of the U.S. National Health Interview Survey. Children were categorized as having asthma if their parents reported that asthma was current at the time of interview and had been present for more than 3 months. Mothers were asked about their smoking habits during and after pregnancy. Odds of having asthma were 2.1 times as high (95% C.I. = 1.3, 3.3) among children of mothers who smoked 10 or more cigarettes per day than among children of nonsmoking mothers. The risk of having asthma was not significantly increased in children of mothers who smoked fewer than 10 cigarettes per day. Use of asthma medication was also more frequent among children of mothers who smoked 10 or more cigarettes per day (OR = 4.1; 95% C.I. = 1.9, 8.9). Results did not change significantly after controlling for gender, race, presence of both parents, family size, and number of rooms in the households. No information was available on parental respiratory symptoms or socioeconomic status. The results of this study could be explained partially by overreporting of asthma by smoking mothers.

Oldigs and collaborators (1991) exposed 11 asthmatic children to ETS and to ambient air for 1 hour. They found no significant difference in lung function or in bronchial responsiveness to histamine after ETS exposure when compared with sham exposure. The study was designed only to determine if acute exposures to ETS caused immediate effects, and it did not assess the changes induced by chronic exposure to ETS.

Martinez and coworkers (1992) studied incidence of new cases of asthma in a population sample of 774 out of 786 eligible children aged 0 to 5 years enrolled in the Tucson study of chronic obstructive lung disease. At the time of enrollment, the child's parents answered standardized questionnaires about personal respiratory history and cigarette smoking habits. Surveys were performed on an approximately yearly basis, and parents were asked if the child had been seen by a doctor for asthma in the previous year. There were 89 (11.5% of the total) new cases of asthma during followup. Children of mothers with 12 or fewer years of formal education and who smoked 10 or more cigarettes per day were 2.5 times as likely (95% C.I. = 1.4, 4.6) to develop asthma as were children of mothers with the same education level who did not smoke or who smoked fewer than 10 cigarettes per day. This relationship was independent of self-reported symptoms in parents. Decrements in lung function paralleled the increase in asthma incidence. No relationship was observed between maternal smoking and asthma incidence among children of mothers with more than 12 years of formal education.

Ehrlich et al. (1992) studied 72 children with acute asthma recruited in the emergency room; 35 nonacute asthmatic children from an asthma clinic; and 121 control children without asthma from the emergency room. They assessed exposure to ETS both by questionnaire and by measurement of urinary levels of cotinine/creatinine ratios. Smoking by maternal caregiver was significantly more prevalent among asthmatic children (OR = 2.0, 95% C.I. = 1.1, 3.4). This was confirmed by a significant difference between groups in prevalence of cotinine to creatinine ratio of greater or equal to 30 ng/mg (OR = 1.9; 95% C.I. = 1.0, 3.4). There was no difference in exposure indices between acute and nonacute asthmatics. The authors concluded that smoking by a maternal caregiver was a significant risk factor for clinically significant asthma in children.

7.6.2. Summary and Discussion on Asthma

There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease. Several studies have found that bronchial responsiveness is more prevalent and more intense among asthmatic children exposed to maternal smoke. Emergency room visits are more frequent in children of smoking mothers, and these children also have been found to need more medication for their asthma than do children of nonsmoking mothers (see Table 7-4).

A simple bronchospastic effect of cigarette smoke is probably not responsible for the increased severity of symptoms associated with passive smoking because acute exposure to ETS has been found to have little immediate effect on lung function parameters and airway responsiveness in asthmatic children. Therefore, the mechanisms by which passive smoking enhances asthma in children who already have the disease are likely to be similar to those responsible for inducing asthma and entail chronic exposure to relatively high doses of ETS (see discussion below). Murray and Morrison (1988) reported that ETS exposure decreased lung function and increased medication requirements in asthmatic children only during the cold, wet season and not during the dry, hot season in Vancouver, Canada. These seasonal differences may be at least partly explained by the finding by Chilmonczyk and collaborators (1990) that urine cotinine levels of children exposed to ETS are significantly higher in winter than in summer. These seasonal fluctuations also suggest that the effects of passive smoking on asthma severity are reversible and that decreasing exposure to ETS could prevent many asthmatic attacks in affected children.

New evidence available since the Surgeon General's report (U.S. DHHS, 1986) and the NRC report (1986) also indicates that passive smoke exposure increases the number of new cases of asthma among children who have not had previous episodes (see Table 7-7 for results and references). Although most studies are based on parental reports of asthma, it is highly unlikely that the relationship between asthma and ETS exposure is entirely attributable to reporting bias. In fact, concordance in the relationship between ETS exposure and both questionnaires and objective parameters such as lung function or bronchial provocation tests has been reported in several studies. The association is also biologically plausible; the mechanisms that are likely to be involved in the relationship between ETS exposure and asthma have been discussed extensively in Section 7.2. The consistency of all the evidence leads to the conclusion that ETS is a risk factor for inducing new cases of asthma. The evidence is suggestive of a causal association but is not conclusive.

Data suggest that levels of exposure required to induce asthma in children are high; in fact, most recent and earlier studies that classified children as exposed to ETS if the mother smoked one cigarette or more usually failed to find any effect of ETS on asthma prevalence or incidence. Furthermore, two recent large studies found an increase in the prevalence (Weitzman et al., 1990) or incidence (Martinez et al., 1992) of asthma only if the mother smoked 10 cigarettes or more per day. It is also important to consider that, for any level of parental smoking, exposure to ETS is higher in children belonging to families of a lower socioeconomic level (Strachan et al., 1989) and that the relationship of maternal smoking to asthma incidence may be stronger in such families (Martinez et al., 1992). Concomitant exposure to other pollutants also may enhance the effects of ETS (Krzyzanowski et al., 1990).

7.7. ETS EXPOSURE AND SUDDEN INFANT DEATH SYNDROME

The relationship between ETS exposure and sudden infant death syndrome (SIDS) was not addressed in either the Surgeon General's report (U.S. DHHS, 1986) or in the NRC report (1986).

Because of the importance of this syndrome as a determinant of infant mortality and because of the available evidence of an increased risk of SIDS in children of smoking mothers, the issue has been added to this report (Table 7-8).

SIDS is the most frequent cause of death in infants aged 1 month to 1 year. Approximately 2 of every 1,000 live-born infants (more than 5,000 in the United States alone each year) die suddenly and unexpectedly, usually during sleep, and without significant evidence of fatal illness at autopsy (CDC, 1989b). The cause or causes of these deaths are unknown. The most widely accepted hypotheses suggest that some form of respiratory failure is involved with most cases of SIDS.

In 1966, Steele and Langworth (1966) first reported that maternal smoking was associated with an increased incidence of SIDS. They studied the hospital records of 80 infants who had died of SIDS in Ontario, Canada, during 1960-1961 and compared them with 157 controls matched for date of birth, sex, hospital at which the child was born, and parity of the mother. Infants of mothers who smoked 1 to 19 cigarettes per day were twice as likely (OR = 2.1; 95% C.I. = 1.1, 3.8) to die of SIDS as were infants of nonsmoking mothers. The odds ratio was 3.6 (95% C.I. = 1.7, 7.9) when infants of mothers who smoked 20 or more cigarettes per day were compared to infants of nonsmoking mothers. The authors reported that the risk of dying of SIDS was higher in low-birthweight infants whose mothers smoked when compared with low-birthweight infants whose mothers did not smoke. However, they made no effort to control for other confounders that were related both to maternal smoking and to SIDS, such as maternal age and socioeconomic status. In addition, they made no reference to the relative roles of in utero exposure to tobacco smoke products and postnatal ETS exposure.

Naeye and collaborators (1976) studied 59,379 infants born between 1959 and 1966 in participating hospitals from several U.S. cities. After meticulous investigation of clinical and postmortem material, they identified 125 of these infants (2.3 per 1,000 live births) as having died of SIDS and compared them with 375 infants matched for place of birth, date of delivery, gestational age, sex, race, and socioeconomic status. Infants of mothers who smoked were more than 50% more likely (OR = 1.6; 95% C.I. = 1.0, 2.4) to die of SIDS than were those of mothers who denied smoking. When compared with the latter, infants of mothers who smoked six or more cigarettes per day were 2.6 times more likely (95% C.I. = 1.7, 4.0) to die of SIDS. The authors made no attempt to distinguish between in utero exposure to tobacco smoke products and ETS exposure after birth.

Bergman and Wiesner (1976) selected 100 well-defined cases of SIDS occurring in white children in King County, Washington. These cases were matched for race, sex, and birth date with 100 controls. Questionnaires were mailed to the mothers of cases and controls, but only 56

Table 7-8. Epidemiologic studies of effects of passive smoking on incidence of sudden infant death syndrome (SIDS)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Steele and Langworth (1966)	80 infants who died of SIDS; 157 matched controls in Ontario, Canada	Maternal report from hospital record at birth	OR = 2.1 (1.1, 3.8) when mother smoked 1 to 19 cig./day; OR = 3.6 (1.7, 7.9) when mother smoked ≥20 cig./day	No control for socioeconomic status or maternal age
Naeye et al. (1976)	59,379 infants born in several U.S. cities	Maternal report from hospital record at birth	OR = 1.6 (1.0, 2.4) for any maternal smoking; OR = 2.6 (1.7, 4.0) for mothers smoking ≥6 cig./day	Controlling for place of birth, date of delivery, gestational age, sex, race, and socioeconomic status
Bergman and Wiesner (1976)	100 cases of SIDS; 100 matched controls in King County, Washington	Maternal questionnaire answered after death (or at equivalent age for controls)	OR = 2.4 (1.2, 4.8); effect only significant for mothers ≤25 yr. (OR = 4.4 [1.7, 11.2])	Independent of maternal education, race, sex, and birth date
Lewak et al. (1979)	44 cases of SIDS	Maternal questionnaire	OR = 4.4 (2.1, 9.2)	No control for possible confounding factors
Malloy et al. (1988)	305,000 births in Missouri	Maternal reports on birth certificate	OR = 1.8 (1.4, 2.2)	Controlling for marital status, maternal age, education, parity, and birthweight

(continued on the following page)

Table 7-8. (continued)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Hoffman et al. (1988)	800 SIDS cases; 1,600 controls (NICHD cooperative study)	Maternal questionnaire	OR = 3.4 ($p<0.005$)	Controlling for age, birthweight, and race
Haglund and Cnattingius (1990)	279,000 births in Sweden	Maternal questionnaire	OR = 1.8 (1.2, 2.6). Heavy-smoking mother: OR = 2.7 (1.9, 3.9)	Independent of birthweight, maternal age, social status, parity, sex, and type of birth
Mitchell et al. (1991)	162 SIDS cases; 3 to 4 times as many controls	Parental questionnaire	Cig./day — OR 1 to 9 — 1.9 (1.0, 3.5) 10 to 19 — 2.6 (1.5, 4.7) ≥20 — 5.1 (2.9, 9.0)	Independent of prenatal care, maternal age, education, marital status, sex, neonatal problems, parity, birthweight, race, season of death, and breastfeeding

[1] 95% confidence intervals in parentheses.

cases and 86 controls returned them. Mothers who did not respond tended to be younger and poorer. A higher proportion of mothers of SIDS victims smoked cigarettes during pregnancy (61% vs. 42%). Infants of mothers who smoked after delivery were 2.4 times as likely (95% C.I. = 1.2, 4.8) to die of SIDS as were infants of nonsmoking mothers. The relationship between postnatal exposure to ETS and SIDS was significantly stronger and only reached statistical significance for mothers aged 25 years or less (OR = 4.4; 95% C.I. = 1.7, 11.2). Infants of mothers aged 25 years or less who smoked 20 or more cigarettes per day were 7.7 times as likely to die of SIDS (95% C.I. = 1.7, 35.4) as were infants of nonsmoking mothers. Effects were independent of maternal education. The authors did not try to determine the independent effects of prenatal and postnatal exposures to maternal smoking on the incidence of SIDS.

Lewak and coworkers (1979) studied all infants who died during the first year of life and who were enrolled in a health plan in Oakland, California. Using predefined criteria, they classified 44 infants (2.3 per 1,000 live births) as having died of SIDS and compared them with the rest of the population for several possible risk factors for SIDS. Mothers of infants who died of SIDS were 4.4 times (95% C.I. = 2.1, 9.2) as likely to be smokers as mothers of infants who survived. Paternal smoking had no significant influence on SIDS frequency. The authors made no effort to control for possible confounding factors, nor did they discriminate between the possible roles of prenatal and postnatal exposure to tobacco smoke products.

Malloy and coworkers (1988) linked birth and death certificates to study possible risk factors for neonatal and postneonatal mortality in over 305,000 singleton white live births in Missouri. They identified 372 infants whose deaths were attributed to SIDS (1.2 per 1,000 live births). Infants whose mothers smoked were 1.8 times as likely (95% C.I. = 1.4, 2.2) to die of SIDS than were infants of nonsmoking mothers. This relationship was independent of maternal marital status, education level, age, parity, and child's birthweight. There were no data available that would have allowed one to differentiate the effects of prenatal and postnatal exposure to tobacco smoke products.

Hoffman and collaborators (1988) reported on the results of the National Institute of Child Health and Human Development Cooperative Epidemiological Study of Sudden Infant Death Syndrome risk factors. They studied 800 SIDS cases and 1,600 control infants collected at six study centers across the United States. Control infants were matched for age only (N = 800) or for age, low birthweight, and race (N = 800). SIDS cases were 3.8 and 3.4 times as likely to have smoking mothers as the first and second control groups mentioned earlier, respectively ($p < 0.005$ for both comparisons). There were no data on prenatal and postnatal exposure to tobacco smoke products.

Haglund and Cnattingius (1990) examined risk factors for SIDS in a prospective study based on more than 279,000 Swedish infants who survived the first week of life. SIDS was reported as the sole cause of death in 190 infants (0.7 per 1,000), and in most cases the diagnosis was confirmed by the results of an autopsy. Infants of mothers who smoked one to nine cigarettes per day were 1.8 times as likely (95% C.I. = 1.2, 2.6) to die of SIDS as were infants of nonsmoking mothers. Infants of mothers who were heavy smokers had an even higher risk (OR = 2.7; 95% C.I. = 1.9, 3.9) of dying of SIDS, suggesting an exposure-response relationship. These findings were independent of birthweight, maternal age, social situation, parity, sex, and type of birth. No information was available regarding smoking in the household by either mother or father after the infant's birth.

Mitchell and coworkers (1991) studied SIDS cases occurring in several health districts in New Zealand between November 1, 1987, and October 31, 1988. After careful assessment of the material available from necropsy, 162 infants were classified as having died of SIDS (3.6 per 1,000 live births). These cases were matched for age with three to four times as many controls. The researchers interviewed the parents and obtained complete information for 128 cases and 503 controls. Information on maternal smoking during pregnancy (as a yes/no variable) was obtained from the obstetric records, whereas information on number of cigarettes smoked by the mother in the 2 weeks preceding the interview was obtained from questionnaires. Mothers of infants who died of SIDS were 3.3 times as likely (95% C.I. = 2.2, 5.0) to smoke during pregnancy as were mothers of controls. The analysis of the relationship between maternal smoking after the child's birth and frequency of SIDS showed clear evidence of a biological gradient of risk. Odds ratios were as follows: 1.9 (95% C.I. = 1.0, 3.5) for mothers who smoked 1 to 9 cigarettes per day; 2.6 (95% C.I. = 1.5, 4.7) for mothers who smoked 10 to 19 cigarettes per day; and 5.1 (95% C.I. = 2.9, 9.0) for mothers who smoked 20 or more cigarettes per day. The association between maternal smoking and SIDS frequency was independent of antenatal care, maternal age, maternal education, marital status, sex, neonatal problems, parity, socioeconomic status, birthweight, gestational age, race, season of death, sleep position at death, and breastfeeding.

In summary, there is strong evidence that infants whose mothers smoke are at increased risk of dying suddenly and unexpectedly during the first year of life. This relationship is independent of all other known risk factors for SIDS, including low birthweight and low gestational age. The finding that there is a biological gradient of risk extending from nonsmoking mothers to those smoking more than 20 cigarettes per day adds to the evidence that exposure to cigarette smoke products is involved in the sequence of events that result in SIDS. Available studies cannot differentiate the possible effects with respect to SIDS of exposure to tobacco smoke products in utero from those related to passive smoking after birth. As explained earlier (Section

7.2.2), both human and animal studies show that maternal smoking during pregnancy may modify and potentiate the effects of postnatal ETS exposure. The relationship between maternal smoking and SIDS is independent of low birthweight, which is the most important known effect of maternal smoking during pregnancy. In addition, the incidence of SIDS is apparently associated with days of higher air pollution levels (Hoppenbrouwers et al., 1981), which could indicate a direct effect of airborne contaminants.

In view of the fact that the cause of SIDS is still unknown, it is not possible to assess the biological plausibility of the increased incidence of SIDS related to ETS exposure. Consequently, at this time this report is unable to assert whether or not passive smoking is a risk factor for SIDS.

7.8. PASSIVE SMOKING AND LUNG FUNCTION IN CHILDREN

The Surgeon General's report (U.S. DHHS, 1986) reviewed 18 cross-sectional and longitudinal studies on the effects of ETS exposure on lung function in children (Table 7-9). The report concluded that "the available data demonstrate that maternal smoking reduces lung function in young children" (page 54). The hypothesis was proposed that passive smoking during childhood, by affecting the maximal level of lung function attainable during early adult life, may increase the subsequent rate of decline of lung function and, thus, increase the risk of chronic obstructive lung disease.

The NRC report (1986) reached similar conclusions after reviewing 12 articles (Table 7-9). The authors' summary asserted that "estimates of the magnitude of the effect of parental smoking on FEV_1 function in children range from 0 to 0.5% decrease per year. This small effect is unlikely by itself to be clinically significant. However, it may reflect pathophysiologic effects of exposure to ETS in the lungs of the growing child and, as such, may be a factor in the development of chronic airflow obstruction in later life" (page 215).

7.8.1. Recent Studies on Passive Smoking and Lung Function in Children

Studies appearing since the 1986 reports are presented in Table 7-10.

Lung function measurements were included in the cross-sectional study by O'Connor and collaborators (1987) described earlier (Section 7.6.1). When compared to 97 nonasthmatic children of nonsmoking mothers (mean age ± SEM = 12.8 ± 0.3 years), 168 nonasthmatic children of smoking mothers (mean age ± SEM = 12.9 ± 0.2 years) had significantly lower mean percentage of predicted FEV_1 (mean ± SEM = 108.0 ± 1.4 vs. 101.4 ± 1.1, respectively, $p < 0.001$) and significantly lower FEF_{25-75} (103.0 ± 2.3 vs. 88.2 ± 1.5, respectively, $p < 0.001$). These effects were independent of personal smoking by the child.

Table 7-9. Studies on pulmonary function referenced in the Surgeon General's and National Research Council's reports of 1986

Study	No. of subjects	Age of subjects	Surgeon General	NRC
Berkey et al. (1986)	7,834	Children (6 to 10)	X	X
Brunekreef et al. (1985)	173	Adult women	X	
Burchfield et al. (1986)	3,482	Infants/children (0 to 10)	X	
Chen and Li (1986)	571	Children/adol. (8 to 16)	X	X
Comstock et al. (1981)	1,724	Adults	X	
Dodge (1982)	558	Children (8 to 10)	X	X
Ekwo et al. (1983)	1,355	Children (6 to 12)	X	
Ferris et al. (1985)	10,000	Children/adol. (6 to 13)		X
Hasselblad et al. (1981)	16,689	Children (5 to 17)	X	X
Kauffmann et al. (1983)	7,818	Adults	X	
Kentner et al. (1984)	1,851	Adults	X	
Lebowitz (1984)	117	Families	X	
Lebowitz and Burrows (1976)	271	Children/adol. (<16)	X	X
Schilling et al. (1977)	816	Children/adol. (<18)	X	X
Tager et al. (1979)	444	Children (5 to 19)		X
Tager et al. (1983)	1,156	Children (5 to 9)	X	X
Tashkin et al. (1984)	1,080	Children (7 to 17)	X	X
Vedal et al. (1984)	4,000	Children (6 to 13)	X	
Ware et al. (1984)	10,106	Children (6 to 13)		X
Weiss et al. (1980)	650	Children (5 to 9)	X	X
White and Froeb (1980)	2,100	Adults	X	

Table 7-10. Recent epidemiologic studies on the effects of passive smoking on lung function in children

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
O'Connor et al. (1987)	97 children (12.8 ± 0.3 yr.) of smoking mothers; 168 children (12.9 ± 0.2 yr.) of nonsmoking mothers in Boston, Massachusetts	Parental questionnaire	Nonsmoking mothers vs. smoking mothers: FEV_1 (% predicted) 108.0 ± 1.4 vs. 101.4 ± 1.1 ($p<0.001$); FEF_{25-75} (% predicted) 103.0 ± 2.3 vs. 88.2 ± 1.5 ($p<0.001$)	Independent of personal smoking habits
Lebowitz et al. (1987)	353 subjects aged 5.5 to 25 yr. in Tucson, Arizona	Parental questionnaire	Smoking mothers vs. non-smoking mothers FVC (residuals) +3.3 vs. -1.4 ($p<0.001$)	Interaction between family history of respiratory illnesses and passive smoking for $V_{max}50\%$ residuals
Tsimoyianis et al. (1987)	132 athletes exposed to ETS; 61 athletes not exposed to ETS	Self-reported exposure to ETS	OR of having low FEF_{25-75} 4.7 (1.1-20.8)	
Kauffmann et al. (1989b)	1,160 French children	Parental questionnaire	Loss of 10 mL of FEV_1, ($p=0.05$); loss of 15 mL/sec of FEF_{25-75} ($p<0.01$)	Independent of sex, town of origin, age, height, weight, and family aggregation of lung function
Chan et al. (1989b)	130 children of low birthweight at age 7 yr. in England	Maternal reports of cigarette smoking	Mean $V_{max}75\%$ (% predicted) in exposed vs. nonexposed 80.7 vs. 91.4 ($p<0.01$)	Independent of sex, birthweight, neonatal respiratory illness, and treatment

(continued on the following page)

Table 7-10. (continued)

Authors	Population studied	ETS exposure assessment	Results[1]	Observations
Dijkstra et al. (1990)	634 children aged 6 to 12 yr. in The Netherlands	Parental questionnaire	Decrease in: FEV_1 (-1.8% [-0.2 to -3.31]); $FEF_{25-75\%}$ (-5.21% [-1.4 to -8.8]); PF (-2.8% [0.6 to -4.8])	Independent of maternal smoking during pregnancy
Strachan et al. (1990)	757 children in Scotland	Salivary cotinine levels	Negative correlation with $FEF_{25-75\%}$ ($p<0.05$) and $V_{max}75\%$ ($p<0.05$)	Approx. 7% difference between maximal exposure and no exposure
Martinez et al. (1992)	774 children enrolled at age 0 to 5 in Tucson, Arizona, and followed for several years	Parental questionnaire	15% lower levels of % predicted $FEF_{25-75\%}$ among children of mothers who smoked and had a low level of education	

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[1] 95% confidence intervals in parentheses.

Lebowitz and coworkers (1987) reported on the results of a longitudinal study of pulmonary function development in Tucson, Arizona. The authors analyzed 1,511 observations over an average followup period of 8.8 years in 353 subjects aged 5.5 to 25 years. The last available lung function value (as residuals after regressing the data with different power functions of age and height) was used as outcome. Residuals for vital capacity were significantly higher among subjects aged 14 years or less at entry whose mothers smoked cigarettes (mean = +3.3 vs. -1.4 among nonexposed subjects, $p < 0.001$). Parental smoking had no direct effect on outcome FEV_1 or $V_{max}50\%$, but showed significant interactions with personal smoking and parental history of airway obstructive diseases in their effects on $V_{max}50\%$; subjects who had started smoking or whose parents had airway obstructive diseases and were exposed to ETS had the lowest $V_{max}50\%$ residuals at the end of followup.

In subsequent reports, Lebowitz and Holberg (1988) and Tager and coworkers (1987) reanalyzed two sets of longitudinal pulmonary function data: the one on which the preceding study from Tucson, Arizona, was based (Lebowitz et al., 1987) and data for children of similar age from East Boston, Massachusetts (Tager et al., 1983). The objective was to determine if the different answers with regard to the effect of maternal smoking (significant for the Boston study; no effect for the Tucson study) were due to the use of different statistical tools. Applying the same multivariable analysis of covariance for both data sets, Lebowitz and Holberg (1988) confirmed the positive effect of maternal smoking of $FEF_{25-75\%}$ with the data from Boston ($p < 0.05$) and the lack of a significant effect of maternal smoking on $V_{max}50\%$ with the data from Tucson, Arizona. A first-order autoregressive model applied by Tager and collaborators (1987) to both data sets showed effects of maternal smoking on FEV_1 with the Boston data but not with the Tucson data. The authors concluded that the most likely factor responsible for the disparate results was the exposure difference in the two populations.

Tsimoyianis and collaborators (1987) compared the prevalence of low levels of $FEF_{25-75\%}$ (< 70% of predicted) in athletes exposed and unexposed to ETS (for more information on this study see Section 7.5.1). Of 132 exposed athletes, 18 (13.6%) had low $FEF_{25-75\%}$ compared with 2 of 61 (3.3%) unexposed athletes (OR = 4.7; 95% C.I.= 1.1, 20.8).

Kauffmann and collaborators (1989b) assessed familial factors related to lung function in a cross-sectional study of 1,160 French children. Levels of lung function (FEV_1 and $FEF_{25-75\%}$) were significantly lower in children with mothers who smoked when compared to those whose mothers were nonsmokers. The authors reported a loss of 10 mL of FEV_1 ($p < 0.05$) and of 15 mL/s of $FEF_{25-75\%}$ ($p < 0.01$) for every gram of tobacco smoked per day by the mother. These associations were independent of sex, town of origin, age, height, weight, and intrafamilial aggregation of lung function. There was no effect of paternal smoking on lung function.

Chan and coworkers (1989b) performed lung function tests in a cohort of 130 children of low birthweight (under 2,000 grams) at 7 years. These authors had previously reported on the respiratory outcome of these same children (see Section 7.5.1). Children of low birthweight whose mothers smoked had significantly lower values of percentage of predicted $V_{max}75\%$ than did low-birthweight children whose mothers did not smoke (80.7% vs. 91.4%, $p < 0.01$). This association was independent of sex, birthweight, neonatal respiratory illness, and treatment. As 92% and 79% of mothers who smoked when the child was 7 years old were smokers before and during their pregnancy, respectively, it was not possible to determine whether the effect of maternal smoking was fetal or postnatal.

The study by Dijkstra and collaborators (1990) has been described earlier (Section 7.5.1). The authors studied, together with respiratory symptoms, lung function and its relationship with indoor exposures to ETS and nitrogen dioxide in a population of 634 Dutch children 6 to 12 years of age. When compared with unexposed children, children exposed to ETS had significantly lower levels of FEV_1 (−1.8%; 95% C.I. = −0.2, −3.3), $FEF_{25-75\%}$ (−5.2%; 95% C.I. = −1.4, −8.8) and Peak Flow (−2.8%; 95% C.I. = −0.6, −4.8). Adjustment for smoking by the mother when she was pregnant with the investigated child removed little of the effect of current ETS exposure on lung function. The authors suggested that this indicated that the associations seen at ages 6 to 12 years were not just mirroring harm that was caused when the children were exposed in utero to tobacco smoke components inhaled by the mother. There was no association between exposure to NO_2 and lung function.

A previously mentioned study by Strachan and coworkers (1990) (Section 7.5.1) included lung function measurements in 757 children. Lung function variables were adjusted for sex, height, and housing characteristics. The authors found a significant negative correlation between salivary cotinine concentrations and levels of $FEF_{25-75\%}$ ($p < 0.05$) and $V_{max}75\%$ ($p < 0.05$). For these indices, the difference between adjusted mean values for the top and bottom quintiles of salivary cotinine was of the order of 7% of the mean value in the children with undetectable levels.

The longitudinal study by Martinez and coworkers (1992) has been reviewed earlier (Section 7.6.1). In addition to their findings on incidence of childhood asthma, these authors reported that, at the end of followup, children of mothers with 12 or fewer years of formal education and who smoked 10 or more cigarettes per day had 15% lower mean values for percentage of predicted $FEF_{25-75\%}$ than did children of mothers of the same level of education who were nonsmokers or smoked fewer than 10 cigarettes per day. Maternal smoking had no effect on percentage of predicted $FEF_{25-75\%}$ values in children of mothers who had at least some education beyond high school. Female children of smoking mothers (≥ 10 cig./day) had 7%

higher vital capacity than did female children of mothers who were nonsmokers or light smokers (< 10 cig./day), and this was independent of maternal education. All differences were still significant after controlling for parental history of respiratory disease.

7.8.2. Summary and Discussion on Pulmonary Function in Children

This report concludes that there is a causal relationship between ETS exposure and reductions in airflow parameters of lung function (FEV_1, $FEF_{25-75\%}$, $V_{max}50\%$, or $V_{max}75\%$) in children. For the population as a whole, these reductions are small relative to the intraindividual variability of each lung function parameter; for $FEF_{25-75\%}$, for example, reductions range from 3% to 7% of the levels seen in unexposed children, depending on the study analyzed. Groups of particularly susceptible or heavily exposed subjects have larger decrements: Exposed children of low birthweight, for example, had 12% lower $V_{max}75\%$ than did children of similar birthweight who were not exposed to ETS (Chen, 1989). Likewise, children of less educated mothers who smoked 10 or more cigarettes per day were shown to have 15% lower mean $FEF_{25-75\%}$ than children of less educated mothers who did not smoke or smoked fewer than 10 cigarettes per day. This stronger effect may be explained by Strachan and coworkers' (1989) finding that children of lower socioeconomic status have higher salivary cotinine levels, for any amount of parental smoking, than do children of higher socioeconomic status.

The studies reviewed suggest that a continuum of exposures to tobacco products starting in fetal life may contribute to the decrements in lung function found in older children. In fact, exposure to tobacco smoke products inhaled by the mother during pregnancy may contribute significantly to these changes, but there is strong evidence indicating that postnatal exposure to ETS is an important part of the causal pathway.

New longitudinal studies have demonstrated that young adults who were exposed earlier in life to ETS are also more susceptible to the effects of active smoking (Lebowitz et al., 1987). In addition, Sherrill and collaborators (1990) showed, in a longitudinal study, that children who entered a longitudinal study with lower levels of lung function still had significantly lower levels later in life. The high degree of tracking shown by these spirometric parameters implies that the decrements in lung function related to passive smoking may persist into adulthood. Although the subsequent rates of decline in lung function of these subjects have yet to be studied in detail, the findings by Sherrill and coworkers (1990) support the idea proposed by the Surgeon General's report (U.S. DHHS, 1986) that, by the mechanisms described above, passive smoking may increase the risk of chronic airflow limitation.

7.9. PASSIVE SMOKING AND RESPIRATORY SYMPTOMS AND LUNG FUNCTION IN ADULTS

Both the NRC report (1986) and the Surgeon General's report (U.S. DHHS, 1986) extensively reviewed the evidence then available on involuntary smoking and respiratory health in adults. The Surgeon General's report concluded that healthy adults exposed to ETS may have small changes on pulmonary function testing but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to ETS alone. The report added that the small magnitude of the effect implied that a previously healthy individual would not develop chronic lung disease solely on the basis of ETS exposure in adult life. It was suggested that small changes in lung function may be markers of an irritant response, possibly transient, to the irritants known to be present in ETS.

The NRC report concluded that it was difficult to document the extent to which a single type of exposure like ETS affects lung function. The report attributed this difficulty to the large number of factors, including other exposures, that affect lung function over a lifetime. The report added that results in adults should be evaluated for possible misclassification of ex-smokers or occasional smokers as nonsmokers, as well as possible confounding by occupational exposures to other pollutants. The authors of the report considered it "unlikely that exposure to ETS can cause much emphysema" (page 212), but that, "as one of many pulmonary insults, ETS may add to the total burden of environmental factors that become sufficient to cause chronic airway or parenchymal disease" (page 212).

7.9.1. Recent Studies on Passive Smoking and Adult Respiratory Symptoms and Lung Function

Six recent studies of respiratory symptoms and lung function in adults are presented in Table 7-11.

Svendsen and collaborators (1987) studied longitudinal data from 1,245 married American men aged 35 to 57 years who reported that they had never smoked. Subjects who had smoking wives had significantly higher mean levels of exhaled carbon monoxide (7.7 vs. 7.1 ppm, $p < 0.001$) but not of serum thiocyanate. These men also had lower levels of age- and height-adjusted FEV_1 (mean difference = 99 mL; 95% C.I. = 5, 192.4 mL). However, those with wives who smoked 20 or more cigarettes per day had higher mean adjusted FEV_1 (3,549 mL) than those with wives who smoked 1 to 19 cigarettes per day (3,412 mL), whereas nonexposed subjects had mean adjusted FEV_1 of 3,592 mL.

Kalandidi and coworkers (1987) studied 103 Greek ever-married women aged 40 to 79 who were admitted in 1982 and 1983 to a hospital in Athens with obstructive or mixed type reduction of pulmonary function, without improvement after bronchodilatation. The women

Table 7-11. Recent epidemiologic studies on the effects of passive smoking on adult respiratory symptoms and lung function

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Svendsen et al. (1987)	1,245 married American nonsmoking men aged 35 to 57 yr.	Subject's report of spouse's smoking habits	FEV_1	Mean difference of 99 mL (5-192 mL)	No dose-response effect
Kalandidi et al. (1987)	103 Greek women with obstructive lung disease aged 40 to 79 yr.; 179 control women; all nonsmokers	Subject's report of spouse's smoking habits	See population studied	OR = 1.9 (1.0, 4.0)	No dose-response effect
Masi et al. (1988)	636 subjects aged 15 to 36 yr.	Subject's report of exposure to ETS	Maximal expiratory flows (MEF); diffusing capacity (DC)	Inverse relationship with ETS exposure at home in men for MEF; with exposure at work in women for DC	Strongest effect in men for exposure before age 17 yr.
Kauffmann et al. (1989a)	2,220 American women aged 25 to 69 yr.; 3,850 French women aged 25 to 59 yr.	Subject's report of spouse's smoking habits	Self-report of respiratory symptoms; lung function	OR = 1.3 for wheezed in U.S. sample; OR = 1.4 for cough and OR = 1.2 for dyspnea in French sample; lower FVC and FEV_1 ($p=0.01$) in French women age ≥40 yr.	Increased risks for respiratory symptoms did not reach statistical significance

(continued on the following page)

Table 7-11. (continued)

Authors	Population studied	ETS exposure assessment	Outcome variable	Results[1]	Observations
Hole et al. (1989)	7,997 subjects aged 45 to 64 yr. in Scotland	Questionnaires answered by household members	Cardiorespiratory symptoms; lung function	No significant increase in risk of symptoms; decrease in FEV_1 (60 mL) when a cohabitee smoked >15 cig./day	
Schwartz and Zeger (1990)	100 student nurses in Los Angeles, California	Questionnaire answered by subject on presence of a smoking roommate	Respiratory symptoms assessed by self-administered questionnaire	Increased risk of having phlegm (OR = 1.4 [1.1, 1.9])	Over-reporting by exposed subjects may bias results

[1] 95% confidence intervals in parentheses.

denied that they had ever been smokers, and their husbands' smoking habits were compared with those of 179 ever-married controls of the same age selected from visitors to the hospital. Patients were 1.9 times more likely to have smoking spouses than were controls (95% C.I. = 1.0, 4.0). However, odds ratios were higher for women whose spouses smoked 20 or fewer cigarettes per day (2.5) than for those whose spouses smoked more than 20 cigarettes per day. The unusually high number of nonsmoking women hospitalized with chronic lung disease in a 2-year period suggests that some could have severe asthma unresponsive to bronchodilators and that the results could in part illustrate exacerbation of symptoms in asthmatic women exposed to ETS.

Masi and coworkers (1988) mailed questionnaires to 818 subjects aged 15 to 35 who had previously performed detailed lung function testing and carboxyhemoglobin (COHb) measurements. A total of 636 subjects responded to the questionnaire, and 293 denied having smoked regularly before the date of the lung function tests. All but five subjects had COHb values below 5 grams %. Questionnaires assessed past and present ETS exposure, both at home and at work. Indices of cumulative exposure to ETS at home and at work were calculated from the number of reported smokers on each location, the smoking conditions reported for each area, and the number of years of exposure. In men, there were significant inverse relationships between cumulative exposure to ETS in the home and maximal expiratory flows at low lung volumes. A more detailed analysis showed that in these subjects, exposure before 17 years of age had the strongest effects on lung function, whereas exposure in the 5 years preceding the lung function tests had no effect on lung function. Exposure at work significantly decreased the diffusing characteristics of the lung in women.

Kauffmann and collaborators (1989a) compared the results obtained from a parallel analysis of the association of passive smoking with respiratory symptoms and lung function in 2,220 American women aged 25 to 69 years and 3,855 French women aged 25 to 59 years. Women were classified according to their personal and current spouse's smoking habits. After adjusting for age, city of origin, educational level, and occupational exposure, ever-passive-smokers (excluding active smokers) had significantly more wheeze than true never-smokers (i.e., never active and with nonsmoking spouse) in the U.S. sample (OR of approximately 1.3; C.I. cannot be calculated). There was a positive trend for French passive smokers to have more chronic cough (OR = 1.4) and dyspnea (OR = 1.2), but both results could be due to chance (95% C.I. = 0.8, 2.4 and 0.9, 1.6, respectively). In both samples, no significant decrease of lung function was observed for passive smokers compared with true never-smokers in the whole sample, although FEV_1/FVC values for ever-passive-smokers tended to be intermediate between those of true never-smokers and ex-smokers or active smokers. French women aged 40 or older who were passive smokers had significantly lower FVC ($p < 0.01$) and FEV_1 ($p < 0.01$) than did true never-smokers, but no such effect was seen among American women of the same age.

Hole and coworkers (1989) studied cardiorespiratory symptoms and mortality in a cohort of 7,997 subjects aged 45 to 64 and followed for 11 years in urban west Scotland. A self-administered questionnaire was used in 1972-76 to assess respiratory symptoms and active smoking by each member of the household. When compared with true never-smokers (i.e., persons who were not active smokers and did not live with an active smoker), passive smokers were invariably at a higher risk of having each cardiorespiratory symptom examined (including infected sputum, persistent sputum, and dyspnea), but all 95% confidence intervals for odds ratios included 1. FEV_1 (adjusted for sex, age, and height) was significantly higher in true never-smokers than in passive smokers ($p < 0.01$), but this effect was mainly due to the low adjusted FEV_1 of passive smokers with high exposure (i.e., exposed to a cohabitee who smoked > 15 cig./day; mean = 1.83 L) when compared with those with low exposure (mean = 1.89 L) or with no exposure (mean = 1.88 L). This study was initiated when there was little concern for the possible ill effects of passive smoking and is based on self-reports of active smoking by cohabitees. It is thus probably not affected by classification bias due to overreporting of symptoms by smokers.

Schwartz and Zeger (1990) studied data from a cohort of approximately 100 student nurses in Los Angeles who kept diaries of acute respiratory symptoms (cough, phlegm, and chest discomfort) and for whom data on exposure to passive smoking and air pollution were available. After controlling for personal smoking, a smoking roommate increased the risk of an episode of phlegm (OR = 1.4; 95% C.I. = 1.1, 1.9) but not of cough. The authors also excluded asthmatics (on the assumption that medication could bias the results) and found that in this case, the odds ratio of having phlegm increased to 1.8 (95% C.I. = 1.3, 2.3). The greater sensitivity of diaries of acute symptoms such as those used herein, compared with the indices of period prevalence of symptoms used in other studies, may have increased the power of this study. However, overreporting by exposed subjects is still a possible source of bias in a study that is solely based on self-report of symptoms.

7.9.2. Summary and Discussion on Respiratory Symptoms and Lung Function in Adults

Recent studies have confirmed the conclusion by the Surgeon General's report (U.S. DHHS, 1986) that adult nonsmokers exposed to ETS may have small reductions in lung function (approximately 2.5% lower mean FEV_1 in the studies by Svendsen et al. [1987] and Hole et al. [1989]). Using modern statistical tools designed for longitudinal studies, new evidence also has emerged suggesting that exposure to ETS may increase the frequency of respiratory symptoms in adults. These latter effects are estimated to be 30% to 60% higher in ETS-exposed nonsmokers compared to unexposed nonsmokers.

Because active smoking causes significant reductions in lung function and significant increases in prevalence of respiratory symptoms (U.S. DHHS, 1984), the reported effects of passive smoking in adults are biologically plausible. From a quantitative point of view, effects of passive smoking on lung function are approximately comparable to those reported for light (< 10 cig./day), male active smokers (Camilli et al., 1987). However, because of the self-selection of smokers and other factors, it is difficult to make direct quantitative comparisons between the effects of active and passive smoking. The process of self-selection is likely to occur among smokers by which more susceptible individuals never start smoking or quit smoking early in life (the "healthy smoker" effect). Therefore, lower lifetime doses may be required to elicit effects among nonsmokers than among smokers. The different nature of ETS and MS also has been discussed in previous chapters and must be taken into account when comparing effects of active and passive smoking.

Several sources of bias and confounding factors need to be considered in studies of the effects of single exposures in adults. Classification bias due to underreporting of active smoking or past smoking may significantly affect the results of these studies. Because there is marital aggregation of smoking (i.e., smokers tend to marry smokers, and nonsmokers are more prone to marry nonsmokers), this source of misclassification is more probable among spouses of smokers and may introduce differential biases in some studies. The resulting small overestimation of effect may be nevertheless substantial for effects that are particularly subtle, such as those described for ETS exposure in adults. In addition, recent public concern with passive smoking may increase the awareness of respiratory symptoms in exposed subjects, who may be thus more prone to report symptoms than are unexposed subjects. Studies using objective measures of lung function obviously are not affected by the latter type of bias.

Adults are exposed to multiple sources of potentially harmful substances during their lifetimes, and it is not always possible to control for the effects of these substances because they often are unknown or unmeasurable. In general, the majority of these exposures should introduce nondifferential error to the studies, which would lead to underestimates of the true effects. For example, a significant nondifferential error may be introduced by ETS exposure during childhood, which is known to cause decrements in lung function (see Section 7.7) that may be carried into adulthood. ETS exposure during childhood also is known to cause childhood respiratory diseases (see Sections 7.3, 7.5, and 7.6). Such childhood respiratory diseases, whatever the cause, also may be reflected in decreased respiratory health in adulthood. These effects have not been accounted for in the studies of ETS exposure and lung function in adults, but it is likely that they would lead to underestimates of the ETS effects in the adult studies.

Conversely, effects of ETS would be overestimated if a certain noxious exposure were more likely to occur among ETS-exposed subjects. In this sense, social factors need to be accurately controlled, because prevalence of smoking is significantly higher among less educated than among higher educated subjects (Pierce et al., 1989). Most reviewed studies have controlled for indices of socioeconomic level in a satisfactory manner. Finally, lifestyles may differ between spouses of smokers and those of nonsmokers, but it is not possible to determine a priori the effect of this confounder on the relationship between passive smoking and respiratory health.

The influence of these factors and sources of bias, together with the subtlety of the effects, may explain the inconsistent and sometimes contradictory results of the studies reviewed in this report. In fact, such variability should be expected, particularly for studies with relatively low power (i.e., low probability of finding a statistically significant difference when a difference really exists). The lack of a dose-response relationship in some studies also may be explained by the multiplicity of uncontrolled factors that may affect lung function.

In summary, recent evidence suggests that passive smoking has subtle but statistically significant effects on the respiratory health of nonsmoking adults.

8. ASSESSMENT OF INCREASED RISK FOR RESPIRATORY ILLNESSES IN CHILDREN FROM ENVIRONMENTAL TOBACCO SMOKE

In the preceding chapter, a review was presented of recently published studies regarding the association between respiratory illnesses in children and environmental tobacco smoke (ETS) exposure. The biological plausibility and the possible pathogenetic mechanisms involved in each group of illnesses included in the chapter also were discussed. The purpose of this chapter is to consider the weight of the evidence as a whole, to analyze in detail possible sources of systematic bias or confounding that may explain the observed associations, and to estimate the population impact of ETS-associated respiratory illnesses.

8.1. POSSIBLE ROLE OF CONFOUNDING

In the review of the available evidence indicating an association (or lack thereof) between ETS exposure and the different outcomes considered in this report, the possible role of several confounding factors was analyzed in detail (see Chapter 7). Such analysis will only be summarized here.

- Other indoor air pollutants (wood smoke, NO_2, formaldehyde, etc.) have not been found to explain the effects of ETS but may interact with it to increase the risk of both respiratory illnesses and decreased lung function in children.
- Many of the studies reviewed in this report and in those of the National Research Council (NRC, 1986) and the Surgeon General (U.S. DHHS, 1986) used either multivariate statistical methods of analysis or poststratification of the sample to control for the possible confounding effects of socioeconomic status. Others controlled for this effect by study design. It can be concluded that socioeconomic status does not explain the reported effects of ETS on children's health, although children belonging to some social groups may be at an increased risk of suffering the effects of passive smoking (see also Section 8.3).
- The effect of parental symptoms on the association between ETS and child health also has been extensively analyzed. It can be concluded that, although parents with symptoms may be more aware of their children's symptoms than are parents without symptoms, it is unlikely that this fact by itself explains the association. In fact, objective parameters of lung function, bronchial responsiveness, and atopy, which are not subject to such sources of bias, have been found to be altered in children exposed to ETS.

- The effects of passive smoking may be modified by several characteristics of the exposed child. Increased risk has been reported in premature infants and infants of low birthweight, infants who are not breast-fed, infants who are kept at home with smoking mothers and not sent to day-care centers, asthmatic children. and children who are active smokers.
- Maternal smoking during pregnancy has significant effects on fetal growth and development and may affect lung growth as well as the immunologic system. However, reports of important effects of paternal smoking on the child's health and studies in which ETS exposure was found to have effects that were independent of in utero exposure indicate that maternal smoking during pregnancy does not explain the relation between passive smoking and child health, but modifies the effects of ETS.

In summary, there are no single or combined confounding factors that can explain the observed respiratory effects of passive smoking in children.

8.2. MISCLASSIFICATION OF EXPOSED AND UNEXPOSED SUBJECTS

The importance of misclassification of exposed and unexposed children has not been addressed and will be analyzed in detail below.

Two possible sources of systematic bias related to subject misclassification are considered. The first is upward bias from the effect of active smoking in children; the second is downward bias due to misreporting and background exposure. Both have also been considered in the assessment of ETS and lung cancer in adults. Adjustment for background exposure will be similar to that presented in Chapter 6, except that data for increased incidence of some ETS-associated respiratory diseases show some evidence of thresholds that must also be taken into account.

8.2.1. Effect of Active Smoking in Children

The possibility needs to be considered that some children may be smokers themselves and that this may happen more often among children of smoking parents than among those of nonsmoking parents. This would bias the results upwards or against the null effect. This source of bias is only applicable to studies of older children; regular active smoking may occur but is rare before early adolescence. A study of third graders in Edinburgh, Scotland, by Strachan and coworkers (Strachan et al., 1989, see Section 7.4.1, for example) showed that salivary cotinine levels compatible with active smoking were found in 6 of 770 children ages 6-1/2 to 7-1/2 years, suggesting only a small potential for bias. Consideration should also be given to the fact that some of the effects described in Chapter 7 (for example, the increased risks for acute respiratory illnesses [Section 7.3] and for cough, phlegm, and wheezing [Section 7.5]) have been found to be stronger in younger children (i.e., those less likely to be active smokers) than in older children. This observed reduced effect with increasing age may be in part due to an age-related increase in misclassification of exposed subjects as "unexposed" (see below), but it is clear that these specific effects of ETS *do not increase with age*, as would be expected if active smoking biased the results of studies of ETS effects in older children. It can thus be concluded that the association between respiratory health in children and ETS is not attributable to active smoking by some children. It has been suggested that active and passive smoking may interact to increase the effects of either exposure separately (Lebowitz and Holberg, 1988). This interaction is biologically plausible, because it is likely that active smoking may be more harmful in children whose lungs have been previously affected by ETS (see Section 7.1).

8.2.2. Misreporting and Background Exposure

Various investigators have measured cotinine levels in body fluids in infants and children and correlated the results with parental reports of ETS exposure. Coultas and coworkers (1987) reported that 37% of children under 5 years of age whose parents were nonsmokers had a salivary cotinine level greater than 0, compared with 32% of children ages 6 to 12 and with 35% of children ages 13 to 17. These authors did not ask parents to report possible sources of ETS exposure for their children other than their own tobacco consumption. Strachan and coworkers' study in 6-1/2- to 7-1/2-year-old children in Scotland (Strachan et al., 1989) showed that 73% of children from households with no smokers had detectable concentrations of cotinine in saliva, whereas only 1 in 365 children from households with one or more smokers had no detectable salivary cotinine. The assay used by Strachan and coworkers was 10 times more sensitive than that used by Coultas and coworkers, and this may explain the larger number of subjects with detectable levels in the former study when compared with the latter.

Greenberg and coworkers (1984) studied cotinine levels in 32 infants in North Carolina with reported exposure to tobacco smoke within the previous 24 hours and in 19 unexposed infants. All subjects were under 10 months old. Urine samples of all exposed infants contained cotinine, whereas all unexposed infants except 2 (11%) had undetectable urine cotinine or levels below those of exposed infants with the lowest levels of urine cotinine. This same group of researchers reported results for a larger sample (433 infants at a mean age of 18 days) of the same population (Greenberg et al., 1989). They found that, of 157 infants who reportedly lived in nonsmoking households and were also not in contact with smokers the previous week, 37 infants

(24%) had cotinine in their urine. They concluded that these infants had contact with tobacco smoke during the previous week and that this contact was unknown to or was not reported by their mothers.

Greenberg and coworkers (1991) followed 152 of the 433 infants originally enrolled and reassessed exposure to ETS (through maternal interviews) and urine cotinine levels when the child was 12.3 ± 0.6 months old. They found a significant increase in the prevalence of tobacco smoke absorption, indicated by excretion of cotinine, during the first year of life (from 53% at a mean age of 3 weeks to 77%). The interviews showed that this was mainly due to an increased exposure to nonhousehold sources of smoke (from 14% to 36%). The proportion of infants who reportedly had no contact with smokers but had cotinine in their urine increased from 24% at 3 weeks to 49% at 1 year of age.

These results indicate that studies relying exclusively on parental questionnaires to ascertain ETS exposure in children may misclassify many exposed subjects as nonexposed. Moreover, the degree of misclassification may increase with the child's age.

The possible consequences of this misclassification of exposure need to be discussed in detail. Nondifferential misclassification (i.e., exposure classification that is incorrect in equal proportions of diseased and nondiseased subjects) biases the observed results toward a conclusion of no effect (Rothman, 1986). The effect of differential misclassification depends on the direction in which misclassification occurs. If true ETS exposure is preferentially reported by parents of diseased subjects (i.e., there is reporting bias), an excess of disease prevalence would be found among exposed subjects when compared with unexposed subjects that is unrelated to any biological effect of ETS. The evidence available clearly indicates that this is a very unlikely explanation for the reported misclassification of ETS exposure in infants and children. In fact, reporting bias cannot explain the substantial increase in "underreporting" of exposure with age. The logical explanation is provided by the finding that exposure to nonhousehold smokers increases significantly with age and parallels the increase in the proportion of subjects who have cotinine in their urine (Greenberg et al., 1991). There is no reason to believe that exposure to smokers may occur preferentially among diseased children, and the contrary may be more reasonable; the increased awareness of the ill effects of ETS inhalation may induce parents to limit contact between their diseased children and nonhousehold smokers. Thus, the net effect of misclassification of exposure, both nondifferential and differential, should be a systematic downward bias or bias toward observing no effect. A correction for the nondifferential misclassification bias of background exposure is made in Section 8.3.

8.3. ADJUSTMENT FOR BACKGROUND EXPOSURE

An important conclusion of the previous discussion is that studies based on parental questionnaires may underestimate the health risk from ETS in children due to underreporting of ETS exposure. The NRC (1986) report on passive smoking adopted the use of cotinine measures to correct for misreporting of ETS exposure for lung cancer effects, and this approach was adapted for use in Chapter 6 of this report. It will also be employed here, with the cotinine ratios, however, based on exposure data in children rather than in adults. The method is based on several assumptions: (1) cotinine concentrations in body fluids of nonsmokers are linearly related to ETS exposure, (2) the excess risk of respiratory illness in subjects exposed to ETS is linearly related to the dose of ETS absorbed, (3) the relationship between ambient and absorbed ETS is linear, and (4) one cotinine determination may adequately represent average childhood exposure to ETS.

As support for assumptions 1 and 2, three recent studies have used body cotinine levels as biomarkers for ETS exposure in children. All three have found significant associations between cotinine levels and respiratory effects in children. Etzel et al. (1992) found a significant relationship between serum cotinine levels and otitis media with effusion for children who attended a day-care facility during the first 3 years of life. Ehrlich et al. (1992), in a study that used questionnaires on maternal caregiver smoking as well as urinary cotinine levels to assess ETS exposure, found that by either measure ETS exposure was significantly associated with both acute and nonacute asthma in children. Furthermore, urinary cotinine levels in asthmatic children showed a highly significant correlation with maternal caregiver smoking status. In the third study, Reese et al. (1992) found urinary cotinine levels significantly ($p < 0.02$) elevated in children admitted to the hospital with bronchiolitis compared with a group of similarly aged children admitted with nonrespiratory illnesses. There was also a highly significant correlation ($p < 0.0005$) between urinary cotinine levels and maternal smoking as determined by questionnaire. Thus, the evidence suggests that questionnaire ascertainment of childhood exposure to ETS and cotinine biomarkers in children are highly correlated with each other and that both correlate with childhood diseases. This information is used to develop the risk assessment models below.

While considerable evidence exists for assumptions 1 through 3 (see also Chapter 3), there is some evidence that assumption 4 may not be entirely warranted, at least for older children. Coultas and coworkers (1990b), in a small study of 9 children from 10 homes with at least 1 smoker, reported that there is considerable variability in cotinine levels in body fluids within individuals exposed to ETS when such levels are repeatedly measured on different days. However, Henderson et al. (1989), doing repeated urinary cotinine measures in preschool children, found stable levels over 4 weeks. Thus, while the method of adjustment is based on group mean body cotinine levels, which apparently reflect household ETS levels well, the intraindividual variability, at least in older children, may subject these means to some error.

Application of the method proposed by the NRC requires some knowledge of Z, the ratio between the operative mean dose level in the "exposed" group, d_E, and the mean dose level in the "unexposed" group, d_N. $RR(d_E)$, the relative risk for the group identified as "exposed" compared with the group identified as "unexposed," is thus given by

$$RR(d_E) = (1+Z^*\beta d_N)/(1+\beta d_N) \qquad (8\text{-}1)$$

where β is the amount of increase per unit dose and $Z > RR(d_E) > 1$. (The "unexposed" group actually contains those with background exposure plus those truly unexposed.)

Several studies are available that could be used for the purpose of estimating Z. Jarvis and coworkers (1985) studied 569 nonsmoking schoolchildren ages 11 to 16 in Great Britain. The investigators reported that, when compared with salivary cotinine levels in children of nonsmoking parents (N = 269), mean levels of salivary cotinine were 3.0 times as high in children whose father smoked (N = 96), 4.4 times as high in children whose mother smoked, and 7.7 times as high in children whose parents were both smokers. Pattishall and coworkers (1985) reported that children from homes with smokers (N = 20) had 4.1 times as high mean levels of serum cotinine as children from nonsmoking families. Black children in the same study, however, had lower values of Z (2.8) than did white children. Coultas and coworkers (1987) found that, among 600 U.S. children up to age 17 years, mean salivary cotinine levels were between 1.3 and 2.6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects, and between 2.9 and 3.5 times as high among subjects exposed to two or more smokers at home as among subjects not exposed to cigarette smokers at home. Strachan and coworkers (1989) reported separate results for 6-1/2- to 7-1/2-year-old Scottish children belonging to families living in their own homes and for those belonging to families living in rented homes. In the former, geometric mean salivary cotinine was 6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects and 16 to 17 times as high among subjects exposed to two or more smokers at home as among unexposed subjects. For children belonging to families living in rented homes, the same ratios were 3 to 5.5 times and 4 to 7 times, respectively.

While these studies show consistent relationships between mean body cotinine levels in children and home smoker occupancy, there is also a wide variability in the estimated Z ratios, ranging from 1+ to 17. These different estimates may have very important effects on the background exposure adjustment and, thus, on the calculation of adjusted relative risks for different studies (see also Chapter 6). For example, for a study in which the observed relative risk (RR) is 2.0 but for which the Z ratio is 3, equation 8-1 can be solved for βd_N, which is the estimated increase in relative risk for the group called "unexposed" but who in fact have been exposed to some recent ETS. Solving, $\beta d_N = 1$. Thus, the adjusted RR for the group identified as "unexposed" would be 2, and the adjusted RR for an "exposed" group compared with a truly unexposed group would be $1 + (3*1) = 4$, i.e., twice the observed risk. For a similar example (observed RR = 2) but with Z = 5, $\beta d_N = 0.3$, the RR for a group identified as "unexposed" in this case would be 1.3, and the adjusted RR for an "exposed" to a truly unexposed group would be 2.67. Finally, if the observed RR is still 2 but Z = 17, $\beta d_N = 0.07$, RR for "unexposed" would be 1.07 and the adjusted RR for exposed children would be 2.13. These results are shown in Table 8-1.

These calculations show that when use of parental questionnaires significantly underestimates their children's exposures to other sources of ETS (other than via the parental ETS) and values of Z are lower (as found in black children by Pattishall and coworkers [1985], and in children of lower socioeconomic status by Strachan and coworkers [1989]), the "true" RR of children exposed to ETS may be considerably underestimated. But perhaps the most important conclusion that may be derived from the above analysis is that exposure to ETS from sources other than smoking parents may be high enough to constitute a significant risk for their health. This may be particularly consequential for children of lower socioeconomic levels, whose nutritional status, crowded conditions at home, and opportunity for contact with biological agents of disease make them a part of the population that is particularly susceptible to respiratory illnesses during infancy and childhood. Available data show that ETS exposure via nonhousehold members in these children, as measured by cotinine levels in body fluids, may be as much as one-third that of children exposed to one smoking parent (Z = 3). In the example presented above (observed RR = 2), the estimate of the adjusted relative risk is 4 for children of smoking parents to the truly unexposed children. However, using the same assumptions, children of *nonsmoking parents* who are exposed to ETS (at background levels found in some of the studies) would have twice as high a risk of developing the illness under study as children truly unexposed to ETS.

A cautionary note about the model is appropriate. Table 8-1 shows that, for observed RR = 2 and Z = 3, the adjusted relative risk is 4. However, as the observed RR and Z get closer together, the behavior of the model becomes erratic. This is shown in Table 8-2. In fact, the model (equation 8-1) becomes undefined if Z is less than or equal to the observed RR, and it reaches some stability only as Z becomes at least 30% to 50% greater than the RR.

Table 8-1. Adjusted relative risks for "exposed children." Adjusted or background exposure based on body cotinine ratios between "exposed" and "unexposed" and equation 8-1

		Z Ratio of body cotinine levels ("exposed"/"unexposed")							
		1.50	2.00	3.00	5.00	7.00	10.00	13.00	17.00
Observed Relative Risks (RR)	1.0	1	1	1	1	1	1	1	1
	1.50	-	3.00	2.00	1.71	1.64	1.59	1.57	1.55
	1.75	-	7.00	2.80	2.15	2.00	1.91	1.87	1.84
	2.00	-	-	4.00	2.67	2.40	2.25	2.18	2.13
	2.50	-	-	10.00	4.00	3.33	3.00	2.86	2.76
	3.00	-	-	-	6.00	4.50	3.86	3.60	3.43

Table 8-2. Behavior variations in adjusted relative risks from equation 8-1 when the observed relative risks and Z ratios are close together

		Z ratio							
		1.50	1.75	2.00	2.25	2.50	2.75	3.00	10.00
Observed Relative Risks (RR)	1.50	-	4.50	3.00	2.50	2.25	2.10	2.00	1.59
	1.75	-3.5	-	7.00	4.38	3.50	3.06	2.80	1.91
	2.00	-2.0	-6.00	-	10.00	6.00	4.67	4.00	2.25
	2.25	-1.5	-3.38	-9.00	-	13.50	7.88	6.00	2.62
	2.50	-1.25	-2.50	-5.00	-12.50	-	17.50	10.00	3.00

Fortunately, the estimates of Z presented above are appreciably greater than the observed relative risk estimates seen in Chapter 7, and in the observed range of both RR and Z, the model yields relatively stable estimates of the adjusted RR. Furthermore, as discussed in Chapter 6, the values of RR and Z are expected to be correlated for each study, i.e., the greater the Z ratio between exposed and unexposed groups in each study, the greater should be the observed RR and the less the effect of the (equation 8-1) adjustment.

If the above model is correct, then exposure of children to ETS other than at home (parental smoking) may be an important risk factor for respiratory illness in childhood. On the other hand, it is also possible that for at least some respiratory illnesses, outside exposure to ETS has relatively little effect, either because outside exposures in younger children tend to be less than those of older children or because there may be a threshold of exposure below which certain respiratory effects may not be expected to occur. For this latter case, equation 8-1 is not an appropriate model, and the observed relative risk would be taken to be the true risk. Both models are addressed in the sections that follow.

8.4. ASSESSMENT OF RISK

Neither the NRC report (1986) nor the Surgeon General's report (U.S. DHHS, 1986) attempted to assess the population or public health impact of the increased risk of respiratory disorders in children attributable to ETS exposure. In this section, estimates will be derived for the number of ETS-attributable lower respiratory tract infections in infants and for the induction and exacerbation of childhood asthma. Quantifying the public health impact of other conditions, such as reduced lung function, coughing, wheezing, and middle ear effusion, is difficult, either because of the lack of overt symptoms or because some necessary U.S. population health statistics are not available. Estimates of sudden infant death syndrome (SIDS) occurrences attributable to ETS will not be made but will be discussed in Section 8.4.3.

For the following quantitative analyses, estimates will be developed in terms of ranges. The ranges are derived by the use of both threshold and nonthreshold (equation 8-1) models, different estimates for population incidence and prevalence, and estimated values of Z and RR from studies reviewed above. Various differences in design, disease definition, and conduct among these studies make them less adaptable to meta-analysis techniques than were the lung cancer studies. To the extent that a less rigorous statistical analysis is attempted here, the ranges should reflect that uncertainty.

8.4.1. Asthma

From the analysis of studies regarding risk for asthma and ETS exposure, it was concluded that passive smoking increases both the number and severity of episodes in asthmatic children. It was further concluded that ETS is a risk factor for new cases among previously asymptomatic children, since the evidence is suggestive, but not conclusive, of a causal association (see Section 7.6). Relative risks for asthma ranged from 1.0 to 2.5 in the studies analyzed, but methodologies differed considerably among studies, and effects were often found only in children of mothers who smoke heavily. Of the four large studies, totaling more than 9,000 children (Burchfield et al., 1986; Sherman et al., 1990; Weitzman et al., 1990; Martinez et al., 1991b), three showed statistically significant risk estimates ranging from 1.7 to 2.5, with the two largest ratios, 2.5 (Martinez et al., 1991b) and 2.1 (Weitzman et al., 1990), coming from comparisons using children of heavily smoking mothers (≥ 10 cig./day) as the exposed group. The third study (Burchfield et al., 1986) had OR = 1.7 for males with two smoking parents, but results were not significant either for girls or for children with one parental smoker. The fourth study (Sherman et al., 1990) (770 children) did not find an effect, but made no effort to assess the effect of heavy smoking by parents, nor was there control for socioeconomic status. Thus, assigning a range of 1.75 to 2.25 for the estimated relative risk of developing asthma for children of mothers who smoke 10 or more cigarettes per day appears reasonable and is within the ranges of observed risk.

The above results suggest two possible scenarios. One scenario is that relatively heavy exposure to ETS is needed to bring on asthma, i.e., there is a threshold of exposure below which effects will not occur. Alternatively, lesser exposures may merely induce fewer effects, not detectable statistically with these study designs. The choice of scenario does not affect the observed relative risk but will affect whether or not an adjustment for background exposure (Z ratio) is appropriate. Under the first (threshold) scenario, the estimates of RR = 1.75 to 2.25 need no adjustment; under the alternative (nonthreshold) scenario, equation 8-1 applies.

Considering the nonthreshold model first, from the discussion in Section 8.3, it can be assumed that values of 3 to 10 may be a reasonable range for estimates of Z (i.e., the ratio of body cotinine levels in children whose mothers smoke heavily to those of children whose mothers do not smoke). Lower values of Z would yield significantly larger estimates of asthma cases attributable to ETS. Based on the above estimates for a range of Z and RR and use of the nonthreshold model, the estimated range of adjusted relative risks for children of mothers who smoke 10 or more cigarettes per day would be approximately 1.91 to 6.00 (see Table 8-3). Transforming relative risks to

Table 8-3. Range of estimates of adjusted relative risk and attributable risk for asthma induction in children based on both threshold and nonthreshold models, and different values for Z.

	Threshold model[1]		Nonthreshold model[2]				
Observed relative risk	1.75	2.25	1.75	2.25	1.75	2.00	2.25
Z = Cotinine ratio (exposed/unexposed)	-	-	10	10	3	3	3
Adjusted relative risk[3]	-	-	1.91[4]	2.62[4]	2.80[5]	4.00[5]	6.00[5]
AR_E[6]	0.43	0.56	0.48	0.62	0.64	0.75	0.83
AR_T[7] (P_I[8]=0.17)	0.07	0.09	-	-	-	-	-
AR_T (P_I[9]=0.26)	-	-	0.12	0.16	0.17	0.20	0.22
ETS-attributable population impact[10]	8,000 to 20,000	10,000 to 26,000	13,000 to 34,000	18,000 to 45,000	19,000 to 46,000	22,000 to 54,000	24,000 to 60,000

[1] Threshold model assumes that heavy ETS exposure (i.e., mothers smoking ≥ 10 cig./day) is required to induce new cases.
[2] Nonthreshold model assumes that all ETS exposure can produce some new cases of asthma.
[3] Equation 8-1 for the nonthreshold model; no adjustment for the threshold model.
[4] Ratio of mean body cotinine levels: Z = 10.
[5] Ratio of mean body cotinine levels: Z = 3.
[6] Attributable risk fraction for the exposed population.
[7] Attributable risk fraction for the total (mixed) population.
[8] Proportion of women of reproductive age who smoke at least 10 cigarettes per day (0.26 × 0.65).
[9] Proportion of women of reproductive age who smoke cigarettes.
[10] Range based on 2 million to 5 million asthmatic children under 18 years old in the United States, and assumes that the number of ETS-attributable new cases at each age is constant.

attributable risks (Rothman, 1986), 48% to 83% of all cases of asthma among children of mothers who smoke 10 or more cigarettes per day may be attributable to passive smoking based on

$$AR_E = 100 * (1 - [1/RR]) \qquad (8\text{-}2)$$

where AR_E is the attributable risk (%) for the exposed population.

Under the assumptions of the threshold model, RR = 1.75 to 2.25 for children of heavily smoking mothers, and the AR_E = 43% to 56% (see Table 8-3); for children of light-smoking mothers, RR = 1 and the $AR_E = 0$.

To calculate the percentage of all cases occurring in a mixed population of exposed and unexposed individuals that is attributable to exposure (AR_T), knowledge of the prevalence of mothers smoking 10 or more cigarettes per day is needed because

$$AR_T = AR_E * P_I \qquad (8\text{-}3)$$

where P_I is the proportion of cases that is exposed (Rothman, 1986). It has been reported that approximately 26% of the population of women of childbearing age smoked in the United States in 1988 (CDC, 1991b) and in 1990 (CDC, 1992b). For the number of cigarettes smoked, Weitzman and coworkers (1990), using the 1981 National Health Information Survey (NHIS), found that approximately 50% of smoking mothers of children ages 0 to 5 years smoke 10 or more cigarettes per day. The 1990 NHIS reports that 78% of smoking women ages 18 to 44 smoke at least 10 cigarettes per day (data courtesy of Dr. Gary Giovino, CDC). We have used an average of 65% to derive the estimates in Table 8-3. Based on these figures and the threshold model, it can thus be estimated that approximately 7% to 9% of all cases of asthma may be attributable to exposure to ETS from mothers who smoke 10 or more cigarettes per day. Estimates of the prevalence of asthma among U.S. children less than age 18 vary from 5% to 10% (Clark and Godfrey, 1983) to 3% to 8% (R. Evans et al., 1987), depending on disease definition. This latter paper uses the data from the 1979-1981 NHIS and derives a population asthma prevalence of 2 million to 5 million. A more recent estimate from the 1989 NHIS is 3.9 million (U.S. DHHS, 1990b). Use of these population prevalence figures and the threshold model provides a range of 8,000 to 26,000 as the annual number of new cases of childhood asthma attributable to mothers who smoke 10 or more cigarettes per day. The confidence in this estimate is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

If the nonthreshold model applies, use of the same prevalence figures leads to a range of 13,000 to 60,000 new cases per year attributable to all ETS exposures (Table 8-3).

While the range of 8,000 to 60,000 is plausible, the existing data are more supportive of the threshold model, which assumes that rather heavy exposures to ETS are required to induce asthma in previously asymptomatic children (Section 7.6.2). Thus, the range of 8,000 to 26,000 will be adopted as the more probable range of new cases among children per year attributable to ETS exposure.

In view of the increased number and severity of asthmatic episodes also caused by ETS, the public health impact of ETS on asthmatic children is considerably greater than the range of estimates for new cases presented above. Shephard (1992), after reviewing several studies, concludes that ETS exposure (from any source) exacerbates preexisting asthma in approximately 20% of patients. If this figure is correct, up to 1 million asthmatic children could be affected. Also, in an earlier study, O'Connell and Logan (1974) found that parental smoking aggravated clinical symptoms of 67% of 265 asthmatic children in the Midwest versus 16% of 137 controls ($p < 0.0001$) and that 10% of 400 asthmatic patients (of both smoking and nonsmoking parents) considered tobacco smoke a major aggravating factor. D. Evans and coworkers (1987) found that passive smoking by asthmatic children in New York City (via presence of smokers in the household) was associated with a mean annual increase of 1.34 emergency room visits per year for asthmatic symptoms, an increase of 63% over asthmatic children from nonsmoking households. Ehrlich et al. (1992), in a study not reviewed by Shephard (1992), found that asthmatics with clinically significant symptoms had both higher cotinine levels than controls ($p = 0.04$) and an OR = 2.0 ($p = 0.03$) for maternal caregivers who smoke. Using this estimate of 2.0 with equation 8-1 and a $Z = 3$ also leads to an attributable risk fraction, AR_T, of 20% (equation 8-3). Multiplying this 20% by the 2 million to 5 million asthmatic children in the United States yields estimates of 400,000 to 1,000,000 whose condition is aggravated by exposure to ETS. Thus, exposure to ETS in general and especially to parental ETS adversely affects hundreds of thousands of asthmatic children.

8.4.2. Lower Respiratory Illness

From the assessment of available data (see Section 7.3), it was concluded that exposure of infants and young children to ETS causes an increased incidence of lower respiratory illness (LRI). An examination of the data in the referenced studies of both Tables 7-1 and 7-2 leads to the conclusion that the observed risk of having LRIs is approximately 1.5 to 2.0 times as high in young children whose mothers smoke as in those whose mothers do not smoke and that the risk is probably higher in infants than in toddlers.

This estimate is also consistent with that of the NRC (1986), which estimated a relative risk of up to 2 for infants who have one or more parents who smoke. The more recent evidence reviewed here strongly suggests that the increased risk due to ETS exposure lasts for at least the first 18 months and decreases after that. Based on this evidence, this chapter estimates a relative risk range of 1.5 to 2.0 for infants and children up to 18 months old who have smoking mothers. It will assume that the increased risk is zero after 18 months.

Based on these findings, and following equation 8-1 with a range of Z = 3 to 10 and RR = 1.5 to 2.0, the adjusted relative risk range becomes 1.6 to 4.0, and AR_E takes the range 38% to 75%. As in the previous section, for equation 8-3, the mixed population attributable risk AR_T takes the range 10% to 20%, again based on 1988 and 1990 estimates of approximately 26% women of childbearing age who smoked (CDC, 1991b, 1992b). Because the estimated mean number of cigarettes smoked by these women is approximately 17 to 20 per day (CDC 1991b, 1992b), it is reasonable to assume that most children of smoking mothers will be exposed. Therefore, the proportion of cases exposed, P_I, is estimated to be 0.26.

It has recently been shown that the incidence of LRIs early in life is approximately 30% (Wright et al., 1991). When the analysis is limited to the first 18 months of life, the population at risk is approximately 5.5 million children. A slight modification of the same algorithms described above yields 150,000 to 300,000 cases of LRIs annually in children under 18 months old attributable to exposure to ETS generated mostly by smoking mothers. For RR = 1.5 and Z = 10, the attributable risk fraction for the exposed population, AR_E, is 0.38, and the attributable risk fraction for the total population, AR, is 0.10. Assuming 3.7 million children less than 1 year old and a 30% incidence of LRI, the ETS-attributable population risk is 110,000. In order to get the incidence rate for the 1.8 million children aged 12 to 18 months, also with 30% incidence, the 110,000 must be subtracted from the 540,000 before multiplying by 0.10. The product of 43,000 is then added to 110,000 to determine the total annual incidence of 150,000 LRIs. For RR = 2.0 and Z = 3 the total annual incidence is about 300,000. Approximately 5% of these LRIs require admission to a hospital (Wright et al., 1989); therefore, it is estimated that 7,500 to 15,000 hospitalizations yearly for LRIs may be attributable to ETS exposure.

While these estimates may appear large, three factors suggest that they are on the low side. First, although these estimates are calculated only for children less than 18 months old, Section 7.3 presents evidence that these ETS-attributed increased risks extend at a decreasing rate up to 3 years of age. Second, no estimates have been calculated for exposure in a smoking father-nonsmoking mother household. Third, these numbers do not take into account the fact that many infants and young children have recurrent LRIs, and therefore, more than one episode of such illnesses may be attributable to ETS in each exposed child.

8.4.3. Sudden Infant Death Syndrome

Because this report concludes that there is an association between maternal smoking and SIDS but is unable to determine the contribution that ETS makes to that association (see Section 7.7), no estimate of ETS-attributable SIDS deaths will be calculated. The Centers for Disease Control (CDC, 1991a) provides an estimate of 702 SIDS deaths attributable to maternal smoking, based on a relative risk of 1.5 for infants of actively smoking mothers. While this report concurs with the numbers and the methodology used to determine that estimate, it is unable to apportion the in utero, lactation, and ETS exposure components of the risk.

8.5. CONCLUSIONS

This chapter has attempted to estimate the impact on the U.S. population of ETS exposure on childhood asthma and lower respiratory tract infections in young children. For new cases of asthma in previously asymptomatic children under 18 years of age, we estimate that 8,000 to 26,000 is a probable range of new cases per year that are attributable to ETS exposure from mothers who smoke at least 10 cigarettes per day. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

While the data are most supportive of a situation in which heavy exposures to ETS are required to induce new cases of asthma, two other scenarios would lead to larger estimates. The first is that even in the absence of smoking mothers, a child could receive heavy ETS exposure from other sources. The second is that lesser ETS exposures induce fewer numbers of new cases, and the increase is not statistically detectable. Under this latter (nonthreshold) scenario, the range of new cases of asthma annually attributable to ETS exposure is 13,000 to 60,000.

This report concludes that, in addition to inducing new cases of asthma, ETS exposure increases the number and severity of episodes among this country's 2 million to 5 million asthmatic children. This chapter considers exposure to parental smoking to be a major aggravating factor to approximately 10%, or 200,000, asthmatic children. Estimates of the number of asthmatics whose condition is aggravated to some degree by ETS exposure are very approximate but could run well over 1 million.

This chapter also estimates that 150,000 to 300,000 cases annually of lower respiratory tract infections in children up to 18 months old are attributable to ETS exposure, most of which comes from smoking parents (mostly mothers). These ETS-attributable cases are estimated to result in 7,500 to 15,000 hospitalizations annually. Confidence in these estimates is high based on the conclusion of a causal association and the strong validity of parental smoking as a surrogate of temporally relevant ETS exposure in infants and young children. Additional cases and hospitalizations are expected to occur in children up to 3 years old in decreasing numbers, but this report makes no further quantitative estimates.

Infants' exposure to ETS may also be responsible for a portion of the more than 700 deaths from SIDS attributable to maternal smoking by the CDC (1991a), but this report is unable to determine whether and to what extent these deaths can be attributed specifically to ETS exposure.

The estimates of population impact presented above are given in ranges and approximate values to reflect the uncertainty of extrapolating from individual studies to the population. As with the lung cancer population impact assessment (Chapter 6), these extrapolations are all based on human studies conducted at true environmental levels. Therefore, they suffer from none of the uncertainties associated with either animal-to-human or high-to-low exposure extrapolations.

In addition to the estimates presented above, ETS exposure in children also leads to reduced lung function, increased symptoms of respiratory irritation, and increased prevalence of middle ear effusion, but this report does not provide estimates of the population impact of ETS exposure for these conditions.

ATTACHMENT 3

United States
Environmental Protection
Agency

EPA 402-F-94-005
June 1994

Setting the Record Straight: Secondhand Smoke is A Preventable Health Risk

Introduction

In early 1993, EPA released a report (*Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders*; EPA/600/6-90/006 F) that evaluated the respiratory health effects from breathing secondhand smoke (also called environmental tobacco smoke). In that report, EPA concluded that secondhand smoke causes lung cancer in adult nonsmokers and impairs the respiratory health of children. These findings are very similar to ones made previously by the National Academy of Sciences and the U.S. Surgeon General.

The EPA report classified secondhand smoke as a Group A carcinogen, a designation which means that there is sufficient evidence that the substance causes cancer in humans. The Group A designation has been used by EPA for only 15 other pollutants, including asbestos, radon, and benzene. Only secondhand smoke has actually been shown in studies to cause cancer at typical environmental levels. EPA estimates that approximately 3,000 American nonsmokers die each year from lung cancer caused by secondhand smoke.

Every year, an estimated 150,000 to 300,000 children under 18 months of age get pneumonia or bronchitis from breathing secondhand tobacco smoke. Secondhand smoke is a risk factor for the development of asthma in children and worsens the condition of up to one million asthmatic children.

EPA has clear authority to inform the public about indoor air pollution health risks and what can be done to reduce those risks. EPA has a particular responsibility to do everything possible to warn of risks to the health of children.

A recent high profile advertising and public relations campaign by the tobacco industry may confuse the American public about the risks of secondhand smoke. EPA believes it's time to set the record straight about an indisputable fact: secondhand smoke is a real and preventable health risk.

EPA absolutely stands by its scientific and well documented report. The report was the subject of an extensive open review both by the public and by EPA's Science Advisory Board (SAB), a panel of independent scientific experts. Virtually every one of the arguments about lung cancer advanced by the tobacco industry and its consultants was addressed by the SAB. The panel concurred in the methodology and unanimously endorsed the conclusions of the final report.

The report has also been endorsed by the U.S. Department of Health and Human Services, the National Cancer Institute, the Surgeon General, and many major health organizations.

Classification of Secondhand Smoke as a Known Human (Group A) Carcinogen

The finding that secondhand smoke causes lung cancer in nonsmoking adults is based on the total weight of the available evidence and is not dependent on any single analysis. This evidence includes several important facts.

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First, it is indisputable that smoking tobacco causes lung cancer in humans, and there is no evidence that there is a threshold below which smoking will not cause cancer.

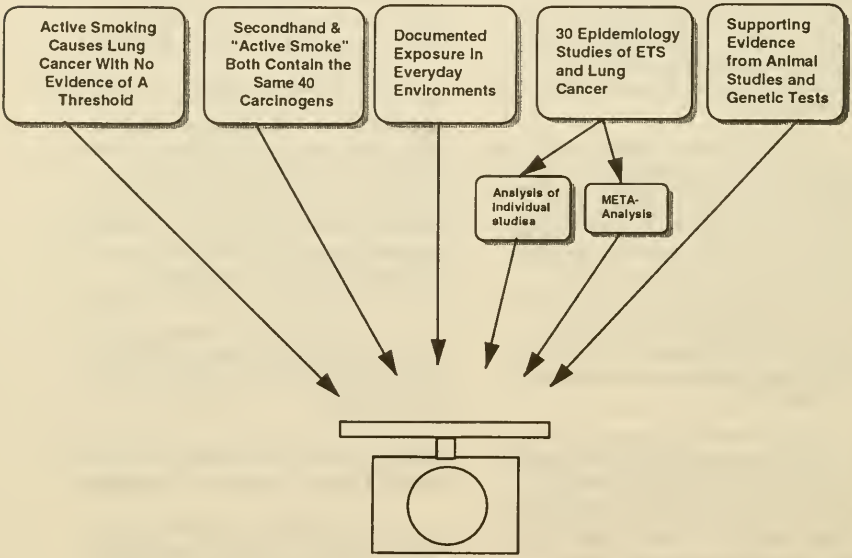
Second, although secondhand smoke is a dilute mixture of "mainstream" smoke exhaled by smokers and "sidestream" smoke from the burning end of a cigarette or other tobacco product, it is chemically similar to the smoke inhaled by smokers, and contains a number of carcinogenic compounds.

Third, there is considerable evidence that large numbers of people who do not smoke are exposed to, absorb, and metabolize significant amounts of secondhand smoke.

Fourth, there is supporting evidence from laboratory studies of the ability of secondhand smoke both to cause cancer in animals and to damage DNA, which is recognized by scientists as being an instrumental mechanism in cancer development.

Finally, EPA conducted multiple analyses on the then-available 30 epidemiology studies from eight different countries which examined the association between secondhand smoke and lung cancer in women who never smoked themselves but were exposed to their husband's smoke. Since the epidemiology studies are the major thrust of the tobacco industry arguments against the EPA report, these studies are examined in more detail below.

WEIGHT OF EVIDENCE FOR CLASSIFYING SECONDHAND SMOKE AS A KNOWN HUMAN (GROUP A) LUNG CARCINOGEN


Active Smoking Causes Lung Cancer With No Evidence of A Threshold
Secondhand & "Active Smoke" Both Contain the Same 40 Carcinogens
Documented Exposure In Everyday Environments
30 Epidemiology Studies of ETS and Lung Cancer
Supporting Evidence from Animal Studies and Genetic Tests
Analysis of individual studies
META-Analysis

The Epidemiology Studies

The most important aspect of the review of the epidemiology studies is the remarkable consistency of results across studies that support a causal association between secondhand smoke and lung cancer.

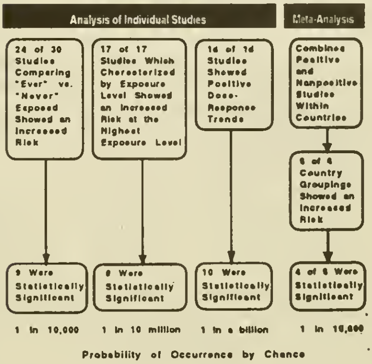
In assessing the studies several different ways, it becomes clear that the extent of the consistency defies attribution to chance. When looking only at the simple measure of exposure of whether the husband ever smoked, 24 of 30 studies reported an increase in risk for nonsmoking women with smoking husbands. Since many of these studies were small, the chance of declaring these increases statistically significant was small. Still, nine of these were statistically significant, and the probability that this many of the studies would be statistically significant merely by chance is less than *1 in 10 thousand*.

The simple overall comparison of risks in ever vs. never exposed to spousal smoking tends to hide true increases in risk in two ways. First, it categorizes many women as never exposed who actually received exposure from sources other than spousal smoking. It also includes some women as exposed who actually received little exposure from their husband's smoking. One way to correct for this latter case is to look at the women whose husbands smoked the most. When one looks at the 17 studies that examined cancer effects based on the level of exposure of the subjects, every study found an increased lung cancer risk among those subjects who were most exposed. Nine were statistically significant. The probability of 9 out of 17 studies showing statistically significant results occurring by chance is less than *1 in ten million*.

Probably the most important finding for a causal relationship is one of increasing response with increasing exposure, since such associations cannot usually be explained by other factors. Such exposure-response trends were seen in all 14 studies that examined the relationship between level of exposure and effect. In 10 of the studies the trends were statistically significant. The probability of this happening by chance is less than *1 in a billion*.

It is unprecedented for such a consistency of results to be seen in epidemiology studies of cancer from environmental levels of a pollutant. One reason is that it is extremely difficult to detect an effect when virtually everyone is exposed, as is the case with secondhand smoke. However, consistent increased risks for those most exposed and consistent trends of increasing exposure showing an increasing effect provide strong evidence that secondhand smoke increases the risk of lung cancer in nonsmokers.

30 EPIDEMIOLOGY STUDIES OF ETS AND LUNG CANCER


Analysis of Individual Studies
Meta-Analysis
24 of 30 Studies Comparing "Ever" vs. "Never" Exposed Showed an Increased Risk
17 of 17 Studies Which Characterized by Exposure Level Showed an Increased Risk at the Highest Exposure Level
14 of 14 Studies Showed Positive Dose-Response Trends
Combines Positive and Nonpositive Studies Within Countries
6 of 6 Country Groupings Showed an Increased Risk
9 Were Statistically Significant
9 Were Statistically Significant
10 Were Statistically Significant
4 of 6 Were Statistically Significant
1 in 10,000
1 in 10 million
1 in a billion
1 in 10,000
Probability of Occurrence by Chance

How Big a Lung Cancer Risk for Adults?

The evidence is clear and consistent: secondhand smoke is a cause of lung cancer in adults who don't smoke. EPA has never claimed that minimal exposure to secondhand smoke poses a huge individual cancer risk. Even though the lung cancer risk from secondhand smoke is relatively small compared to the risk from direct smoking, unlike a smoker who chooses to smoke, the nonsmoker's risk is often involuntary. In addition, exposure to secondhand smoke varies tremendously among exposed individuals. For those who must live or work in close proximity to one or more smokers, the risk would certainly be greater than for those less exposed.

EPA estimates that secondhand smoke is responsible for about 3,000 lung cancer deaths each year among nonsmokers in the U.S.; of these, the estimate is 800 from exposure to secondhand smoke at home and 2,200 from exposure in work or social situations.

The Risks to Children are Widely Acknowledged

The conclusion that secondhand smoke causes respiratory effects in children is widely shared and virtually undisputed. Even the tobacco industry does not contest these effects in its media and public relations campaign.

EPA estimates that every year, between 150,000 and 300,000 children under 1-1/2 years of age get bronchitis or pneumonia from breathing secondhand tobacco smoke, resulting in thousands of hospitalizations. In children under 18 years of age, secondhand smoke exposure also results in more coughing and wheezing, a small but significant decrease in lung function, and an increase in fluid in the middle ear. Children with asthma have more frequent and more severe asthma attacks because of exposure to secondhand smoke, which is also a risk factor for the onset of asthma in children who did not previously have symptoms.

Other Risks

Secondhand smoke contains strong irritants and sensitizers and many adults, as well as children, suffer irritation and other acute effects whenever they are exposed to secondhand smoke. In addition, there is mounting evidence that exposure to secondhand smoke can have an effect on the cardiovascular system, although the EPA report does not address this issue.

Tobacco Industry Media Campaign

The tobacco industry is raising numerous issues which may distract the public from the fact that secondhand smoke poses a real and preventable health risk. The tobacco industry neither acknowledges nor disputes EPA's conclusions of respiratory effects in children. It focuses instead on EPA's findings on lung cancer.

The overall thrusts of the tobacco industry's arguments are that EPA manipulated the lung cancer data to come to a predetermined conclusion. The industry also argues that a nonsmoker's exposure to secondhand smoke is so small as to be insignificant. The argument on minimal exposure is belied both by the acute irritation and respiratory effects and the fallacy of the "cigarette equivalents" approach discussed below. Responses to the specific criticisms of EPA's assessment of the lung cancer data follow.

The 11 U.S. Lung Cancer Studies

Critics of the EPA report argue that by normal statistical standards, none of the 11 U.S. studies included in the EPA report showed a statistically significant increase in the simple overall risk measure, and that EPA should therefore have been unable to conclude that secondhand smoke causes lung cancer in nonsmokers. These critics are misrepresenting a small part of the total evidence on secondhand smoke and lung cancer.

The consistency of study results in the highest exposure category and exposure-response trends discussed above also apply to the U.S. studies. For example, seven of the 11 U.S. studies had fewer than 45 cases, making statistical comparisons difficult. Nonetheless, eight of the 11 had increased overall risks, and for the seven studies which reported on risks by amount of exposure, the highest exposure groups in all seven had increased risks. While the 11 U.S. studies are not, by themselves, conclusive, they do support the conclusion that secondhand smoke is causally associated with lung cancer.

Studies Completed Since Release of the EPA Report

Critics claim that had EPA not "excluded" the recent Brownson study, the Agency could not have concluded that secondhand smoke causes cancer. In fact, four new lung cancer epidemiology studies, including the Brownson study, have been published since the literature review cutoff date for the 1993 EPA report, and all support EPA's conclusions. Three of these are large U.S. studies funded, at least in part, by the National Cancer Institute. A 1992 study of Florida women by Stockwell et al. found a 60% overall increased risk of lung cancer from exposure to their husband's smoke, with significant results for both the highest exposure group and the exposure-response trend. The 1992 study of Missouri women by Brownson et al. found no overall increased risk, but did demonstrate a significant increase in risk in the highest spousal smoking exposure group and a positive exposure-response trend.

The 1994 study by Fontham et al. of women in two California and three Southern cities is the largest case-control study on the subject ever conducted and is considered by EPA to be the best designed study on secondhand smoke and lung cancer conducted to date. This study found significantly increased risks for overall exposure and in the highest exposure group and a strong positive exposure-response relationship. These findings were significant not only for exposure from spouses, but also for exposure in the workplace and in social situations.

90% vs 95% Confidence Intervals

Critics of the EPA report have charged that EPA changed the confidence interval in order to come to a predetermined conclusion. However, the conclusion that secondhand smoke is a known human carcinogen simply does not hinge on whether or not a 95% or 90% "confidence interval" was used. A confidence interval is used to display variability in relative risk estimates in the epidemiology studies. As discussed above, the Group A designation is based on the total weight of the available evidence. The consistency of results that are seen in the numerous studies examined lead to a certainty of greater than 99.9% that secondhand smoke increases the risk of lung cancer in nonsmokers.

Use of what is called in statistics a "one-tailed test of significance," which often corresponds to a 90% confidence interval, is a standard and appropriate statistical procedure in certain circumstances. The "one-tailed test" is used when there is prior evidence that if there is an effect from a substance, it is highly likely to be an adverse rather than a protective effect, or vice versa. In the case of secondhand smoke, an extensive database exists for direct smoking indicating that if chemically similar secondhand smoke also has a lung cancer effect, this effect is likely to be similarly adverse. EPA used one-tailed significance tests for lung cancer in both external drafts of the risk assessment document as well as the final report. Ninety percent confidence intervals were also used in other EPA cancer risk assessments, including methylene chloride, coke oven emissions, radon, nickel, and dioxin.

In the non-cancer respiratory effects portions of the report, "two-tailed tests" and 95% confidence intervals were used, since there was less prior evidence from smokers to suggest that secondhand smoke would cause bronchitis, pneumonia, and ear infections in children.

The Meta-analysis

Meta-analysis was used for the lung cancer data as an objective method of combining results from many studies and was specifically endorsed by the SAB for use with this database. Some critics argue both that the meta-analysis was not an appropriate technique, and that had EPA included the Brownson study (addressed above) in the meta-analysis of overall spousal exposure, EPA could not possibly have classified secondhand smoke as a known human carcinogen. This just isn't true.

The finding that secondhand smoke is a known cause of lung cancer in humans is based on all the evidence and is not dependent on the meta-analysis of the simple ever- vs. never- exposed comparisons, as the critics suggest. If the meta-analysis were removed from the report entirely, the findings would be precisely the same. The meta-analysis was used primarily for estimating and quantifying the population risks from exposure to secondhand smoke, and an alternative approach also used in the report gave very similar results.

Confounders

In the secondhand smoke report, a confounder would be a specific factor that could be responsible for the lung cancer increases observed in nonsmokers instead of secondhand smoke. The tobacco industry and its consultants have suggested, for example, that nonsmoking wives might share in the same poor dietary habits as their smoking husbands, increasing their risk.

The consistency of results across different countries where lifestyle factors, including diet, vary, argues against confounding. For example, while the tobacco industry theorizes that a high fat diet is a confounding factor, the studies from Japan, where dietary fat intake is among the lowest in the world, show a strong dose-response relationship for secondhand smoke and lung cancer.

The EPA report did examine the available data for six potential confounders such as occupation, dietary factors, and history of lung disease, and concluded that none was likely to explain the lung cancer increases seen in the studies.

The 1994 Fontham et al. study controlled for diet and other potential confounders, and concluded, "These observations indicate that the strong association in this study between adult secondhand smoke exposure and lung cancer risk cannot be attributed to any likely confounder."

The "Threshold Theory"

Although some have argued that tobacco smoke cannot cause cancer below a certain level, there is no evidence that this threshold exists. In the absence of such evidence, carcinogens at any level are considered by EPA to increase risk somewhat, although the degree of risk certainly is reduced as exposure decreases. The increased risks observed in the secondhand smoke epidemiology studies are further evidence that any threshold for secondhand smoke would have to be at very low levels.

"Cigarette Equivalents"

The tobacco industry uses the "cigarette equivalent" method of comparing smokers' and nonsmokers' exposures to a single component of tobacco smoke to infer that a nonsmoker's exposure to tobacco smoke is insignificant. However, the cigarette equivalent method has no scientific support, and was rejected by the SAB panel that reviewed the EPA report. Among the many problems with this method is the fact that while secondhand smoke and mainstream smoke contain the same approximately 4,000 compounds, their ratios of individual compounds differ by factors in the thousands. Thus, there is no single compound in tobacco smoke that is an adequate indicator for drawing such comparisons. An RJ Reynolds newspaper ad, while utilizing the method, acknowledges it may not be relevant for assessing risk from secondhand smoke.

Residential Exposures Translated to the Workplace

The tobacco industry frequently argues that because most studies were based on residential exposures, secondhand smoke has not been shown to be a hazard in the workplace. A substance capable of causing cancer in one environment is certainly capable of causing it in any other environment where exposures are comparable, as is the case with residential and workplace exposure to secondhand smoke. In fact, the 1994 Fontham study found a slightly higher risk for workplace exposure than for residential exposures.

The Congressional Research Service (CRS) Report

The RJ Reynolds' media campaign cites a report prepared by the Congressional Research Service (CRS) on cigarette taxes to fund health care reform to argue that CRS believes that the epidemiological evidence on secondhand smoke and health effects is "weak and uncertain." However, CRS has not taken a position on either EPA's risk assessment or the health effects of passive smoking.

Two economists from CRS, citing material largely prepared by the tobacco industry, included a discussion of EPA's risk assessment in an economic analysis of a cigarette excise tax proposal to fund health care reform. In EPA's view, the CRS economists' cursory look at the issues is not comparable to the exhaustive analyses and rigorous review process which EPA undertook when examining the extensive database on secondhand smoke and respiratory health. EPA is confident that a comprehensive analysis of the secondhand smoke database by expert scientists from CRS, with adequate peer review, will come to conclusions about the risks of secondhand smoke similar to those of EPA and many other organizations.

Cigarette Prohibition

The claim that the government is attempting to bring back prohibition -- this time for cigarettes -- is a complete fabrication and utter nonsense. EPA's interest is to provide information to protect the nonsmoker from involuntary exposure to a hazardous substance. Having a choice to take a risk for themselves should not permit smokers to impose a risk on others.

Secondhand Smoke Legislation

Congress has recently passed, and President Clinton has signed into law, legislation restricting smoking in nearly all public places where federal assistance is provided for services to children. Children exposed to secondhand smoke almost never have a choice. Protecting children from the health effects of secondhand smoke should be a priority for everyone.

The Clinton Administration supports pending legislation (H.R. 3434, S.1680, S. 262) that would protect nonsmokers, including children, from secondhand smoke in most public places. These bills would not take away the smoker's freedom to choose to smoke, nor would it bring government regulation into the home.

The bills would also make good economic sense. EPA estimates that smoking restrictions would result in saving $4 billion to $8 billion per year in housekeeping and maintenance expenses.

Perhaps most importantly, the bills would prevent thousands of premature deaths of nonsmokers per year and reduce the incidence of respiratory illness in children.

For Further Information

For additional information on secondhand smoke and other indoor air pollutants, call EPA's Indoor Air Quality Information Clearinghouse.

IAQ
INFO
1(800)438-4318

ATTACHMENT 4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 23 1994

OFFICE OF
RESEARCH AND DEVELOPMENT

Dr. Dan Mulhollan
Director
Congressional Research Service
Library of Congress
First and Independence, S.E.
Washington D.C. 20540-7000

Dear Dr. Mulhollan:

I am writing to express misgivings about the discussion of environmental tobacco smoke (ETS) in the recent Congressional Research Service (CRS) report entitled "Cigarette Taxes to Fund Health Care Reform: An Economic Analysis" (94-214E). Specifically, we disagree with CRS statements that "[t]he link between passive smoking and disease is uncertain" (CRS-7) and that "the epidemiology evidence for passive-smoking-related disease is weak" (CRS-13). The appraisal by CRS economists of the scientific evidence about the effects of ETS on non-smoking adults, and on infants and children, is being widely quoted as an authoritative scientific opinion of CRS. This is unfortunate since the CRS has not taken a position on the health effects of passive smoking, and the economists were careful to state in a May 11, 1994 Senate hearing that this science is outside of their area of expertise. The 1986 ETS reports of the U.S. Surgeon General, and the National Academy of Sciences, as well as the 1992 Environmental Protection Agency report, all concluded that ETS is a significant public health hazard and received extensive peer review before their issuance. Peer review of discussions of the science in the CRS report would have been helpful and inportant since the report raises questions about methods and interpretations that have already been subjected to extensive peer review, some in the review of the EPA report, others in the reviews of all three reports.

The attachment to this letter brings to your attention our views with respect to the CRS statements about the EPA assessment and its results. In addition the attachment notes alternative views about scientific (not economic) aspects of weighing health effects of ETS in the economic analysis. The following points are elaborated in the attachment:

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The epidemiology data on ETS and lung cancer show a remarkable consistency supporting a causal association between ETS and lung cancer in nonsmoking adults. The observed increased risk estimates are not large, but are significant for an environmental exposure, especially considering the inherent difficulties of studying the effects of a mixture to which virtually everyone is exposed at some level. Such difficulties are very likely to hinder the ability to detect an effect if one exists. To observe consistent, though relatively small, increases supported by exposure-response trends, in a variety of countries is highly significant, particularly considering the difficulties involved in conducting these types of studies. For these reasons, it is erroneous to conclude that the overall evidence for an effect is weak simply based on the size of observed increases between spousal smoking and lung cancer. Accepted epidemiology criteria for causality such as consistency, dose-response relationships, biological plausibility, specificity, and temporality, are clearly met by the ETS database.

The EPA report assesses over 100 original studies in reaching its finding that ETS causes several respiratory effects in children. It is difficult to understand the CRS report's summary statement, made without analysis, that "many of the statistical concerns with respect to lung cancer also apply to respiratory effects in children" (CRS-49), since the statistical methods and scientific issues are quite different in the analysis of cancer from those in the analysis of respiratory effects.

Many other organizations also have concluded that the evidence that ETS causes significant health hazards is, in fact, quite strong. These organizations include the National Academy of Sciences (1986), the U.S. Surgeon General (1986), the National Cancer Institute (1993), the National Institute of Occupational Safety and Health (1991), and many public health organizations.

We believe the attached discussion can be helpful in your further consideration of this health issue.

Sincerely yours,

Gary J. Foley
Acting Assistant Administrator
for Research and Development

Attachment

ATTACHMENT

A. EPA's Scientific Approach

- A.1. Lung Cancer
- A.2. Noncancer Respiratory Disorders

B. Public and Scientific Reviews of the EPA Report

C. Differences in Analysis, Process, and Documentation between the EPA and CRS Reports

D. Critique of CRS Criticisms of the EPA Report

E. EPA Comments on the Health Effects Components of the CRS Assessment of Costs due to Passive Smoking

A. EPA's SCIENTIFIC APPROACH

EPA's methodology for hazard identification of health effects is based on a total weight-of-evidence approach, which encompasses evidence on exposure, physical and chemical properties, and toxicology, including animal and human studies. Because environmental tobacco smoke (ETS) contains over 4,000 individual components, including over 40 known human and animal carcinogens, examining components individually would be prohibitive. Instead, ETS was evaluated as a complex mixture. Also, the analysis focused on the respiratory system since that provided the largest database.

The methodologies used for the assessment of lung cancer and noncancer respiratory effects in the EPA report differ. First, lung cancer is only seen in adults and is thought to represent the effect of long-term exposure. The noncancer respiratory effects examined are most apparent in children, and some of these are irritation effects associated with acute exposures. Second, for lung cancer less is known about mechanisms than is the case for some of the childhood respiratory effects, and this leads to differences in the development of the evidence. Third, because there were 30 studies on lung cancer and ETS, this database was analyzed several different ways before arriving at an overall conclusion. For the various childhood respiratory effects that were examined, there were fewer studies of any one effect, and analysis was more limited.

For all effects, studies examine home smoking patterns as a surrogate for ETS exposure. The exposure surrogate in the studies of lung cancer among nonsmokers is spousal smoking patterns. For childhood respiratory effects, parental smoking is the most common surrogate, although recent studies have also shown high correlations between body metabolites of ETS and pneumonia, bronchitis, asthma, and fluid in the middle ear.

There is nearly universal exposure to ETS, which often clouds the distinction between "exposed" and "unexposed" subjects and makes any potential effects difficult to observe. To try to eliminate the effect of some of these misclassified exposures, two methods are used. For hazard identification purposes, trend analysis and analyses comparing high exposure groups with controls are conducted. For population risk estimates, a model which adjusts for background (i.e., non-home) exposures is used.

A.1. Lung Cancer

The conclusion that ETS is a human lung carcinogen is based on the total weight of the available scientific evidence. This evidence includes:

- the strong exposure-response relationships for active smoking for all 4 major lung cancer types, with no evidence of an exposure threshold;
- the chemical similarity of mainstream smoke and ETS, both of which contain over 40 carcinogens;
- supporting evidence from animal bioassays and genotoxicity studies;
- evidence of ETS exposure and uptake by nonsmokers; and
- data from 30 epidemiology studies of ETS and lung cancer from 8 different countries.

The epidemiology studies attempt to estimate the relative risk of lung cancer from actual environmental levels of ETS. Such investigations are inherently difficult for a variety of reasons, not the least of which is the fact that virtually everyone is exposed to some level of ETS from a variety of different sources. Therefore, the studies try to compare risks in people with greater versus lesser exposures. All 30 epidemiology studies provide data on female never-smokers classified as "exposed" or "unexposed" on the basis of whether or not their husbands smoke. Although spousal smoking status is the best single measure of ETS exposure, it is a crude measure, and the studies are prone to exposure misclassification which decreases their ability to detect an increased risk if one exists. Furthermore, many of the studies are of small size and have a low statistical power to detect an increased risk. Despite these difficulties, which make it likely that most studies will not detect an effect if it exists, analysis of the studies reveals consistent evidence linking ETS and lung cancer.

In the EPA report, the epidemiologic data are analyzed a variety of different ways, and each analysis demonstrates an association between ETS and lung cancer. First, the studies were analyzed individually. Using the crude "exposed" versus "unexposed" measure, 24 of the 30 studies found an increased risk of lung cancer in the exposed group; nine of these were statistically significant. This proportion (9/30) of significant studies is highly unlikely to have occurred by chance (probability < one in 10 thousand). In addition, all 17 studies with data categorized by exposure level (i.e., amount of spousal smoking) found an increased risk of lung cancer in the highest exposure group, and 9 of the 17 were statistically significant (probability < one in 10 million), despite the fact that most had a small sample size. Examining only the highest exposure group helps to minimize exposure misclassification in the "exposed" group, since women whose spouses smoke a lot are more likely to be exposed to substantial amounts of ETS. Finally, 10 of the 14 studies with sufficient data for a trend test showed a statistically significant exposure-response relationship (probability < one in a billion), i.e., increasing risk of lung cancer with increasing ETS exposure.

The study data were also combined by country, using a statistical procedure called "meta-analysis" to pool the data. Combining datasets increases the ability to detect an effect, if one is present, and provides an objective means of including all studies, both with positive and non-positive results, in the analysis. This combined analysis also showed increased risks, consistent with the analyses of the individual studies.

A number of potential modifying factors, such as diet and occupation, were also examined, and it was determined that they could not account for the observed increased risks. Furthermore, the consistency of the results across numerous independent studies from different countries argues against the existence of any one factor other than exposure to ETS as an explanation for the observed results.

In summary, the total weight of the evidence is strongly supportive of a conclusion that ETS causes lung cancer in humans, and this conclusion was unanimously endorsed by EPA's Science Advisory Board.

The population risk estimate of approximately 3,000 lung cancer deaths per year in U.S. nonsmokers is based on the pooled relative risk estimate for the 11 U.S. epidemiology studies on ETS and lung cancer, with an adjustment for other sources of ETS exposure in addition to spousal smoking. The adjustment uses biological markers of ETS exposure to assess relative ETS exposure between nonsmokers, with and without spousal exposure. The estimate of 3,000 is consistent with estimates generated in an alternative analysis based on the Fontham et al. study. This NCI-funded multicenter study was the largest U.S. case-control study and is considered representative of the U.S. population. It was designed specifically to examine ETS and lung cancer and pays special attention to eliminating smoker misclassification bias. Furthermore, it is the only study which provided data on both relative risk and relative exposure.

The overall estimate of approximately 3,000 lung cancer deaths is a composite of estimates of 1,500 for female never-smokers, 500 for male never-smokers, and 1,000 for long-term former smokers of both sexes. (These estimated 1,000 ETS-attributable lung cancer deaths in long-term former smokers are in addition to any lung cancer deaths resulting from former smoking.) To extend the analyses of female never-smokers to male never-smokers and to long-term former smokers, the estimated relative risks were converted to excess risks, and these excess risks were assumed to apply to the male never-smokers and the former smokers. This assumption may underestimate the risk in male never-smokers and long-term former smokers, since, for example, males are exposed to greater levels of background ETS. An alternate breakdown of the estimated 3,000 lung cancer deaths attributes 800 deaths to "spousal" (or home) exposure and 2,200 deaths to other sources of exposure, such as work and public places. EPA has relatively high confidence in these estimates, especially those for female never-smokers, since they are based on increased risks observed in humans exposed to ETS at actual environmental levels--there is no extrapolation from high to low dose and no extrapolation from animals to humans.

The epidemiology data on workplace exposure were not included in the report for several reasons. The database is much smaller than the database for females and spousal smoking, with only 10 of the 30 studies reporting data for workplace exposures, and only two reporting risk by levels of exposure. Furthermore, workplace exposures are much more variable over time, with study subjects and their coworkers typically changing jobs several times during a lifetime. Recall of coworkers' smoking habits is less reliable than that of spousal habits; similarly, workers may not be aware of ETS exposures occurring through workplace ventilation systems. The data on female never-smokers and spousal smoking provide the largest database for the purposes of analyzing comparable data, and spousal smoking is a major source of ETS exposure that is relatively stable over time. The inference can be made that if exposure to ETS at home can cause lung cancer, then exposure to comparable levels of ETS in other indoor environments can also cause lung cancer. The EPA report documents exposure studies showing that ETS levels in workplaces where smoking occurs are comparable to levels in homes where smoking occurs.

A.2. Noncancer Respiratory Disorders

The weight of evidence for the noncancer respiratory disorders includes mechanistic information on tobacco smoke's effects on the lung, as well as data from over 100 epidemiological studies. Both maternal smoking during pregnancy and postnatal exposure to ETS can predispose a child to a variety of respiratory effects that can themselves have long-term consequences. Maternal smoking during pregnancy can affect the developing lung, causing permanent changes in lung structure and function, e.g. decreased lung elasticity. Postnatal exposures to ETS may similarly affect lung development, as well as increase bronchial responsiveness and enhance the process of allergic sensitization of the lung. These changes may predispose children to acute lower respiratory tract infections early in life, and to asthma, lower levels of lung function, and chronic airflow limitation later in life.

Epidemiology studies have consistently demonstrated increased risks of lower respiratory tract infections in young children whose parents smoke. In addition, epidemiology studies of children show that ETS exposure is causally associated with increased prevalence of fluid in the middle ear, symptoms of upper respiratory tract irritation (e.g., coughing and wheezing), and reductions in lung function. ETS exposure is also causally associated with additional episodes and increased severity of symptoms in children with asthma. Furthermore, the data are suggestive that ETS exposure can cause new cases of asthma in children who have not previously displayed symptoms; however, there were too few studies to make a conclusive determination. No conclusions could be drawn about upper respiratory tract infections (i.e., colds and sore throats) or middle ear infections in children. The epidemiology studies of noncancer respiratory disorders in nonsmoking adults generally relied on spousal smoking as a surrogate for ETS exposure, and also demonstrated significant effects, including coughing, phlegm production, chest discomfort, and reduced lung function.

Because of the widespread exposure to ETS and the high incidence rates for respiratory illnesses and disorders, even small increases in risk can result in substantial numbers of cases being attributable to ETS. For example, acute lower respiratory tract infections are one of the leading causes of morbidity and mortality during infancy and childhood, and the EPA report estimates that ETS exposure is responsible for 150,000 to 300,000 cases in children up to 18 months, resulting in 7,500 to 15,000 hospitalizations, each year. Fluid in the middle ear is another common affliction in young children and is the most common reason for hospitalization of young children for an operation. As a final example of the public health impacts of ETS exposure, the EPA estimates that as many as one million asthmatic children have their condition worsened by exposure to ETS.

B. PUBLIC AND SCIENTIFIC REVIEWS OF THE EPA REPORT

A first external draft of this assessment was released for public review and comment in June 1990. In December 1990, EPA's Science Advisory Board (SAB), a committee of independent outside scientific experts in the field, conducted a review of the draft report and submitted its comments to the EPA Administrator in April 1991. In its comments, the SAB's Indoor Air Quality/Total Human Exposure Committee concurred with the primary findings of the report, but made a number of recommendations for strengthening it.

Incorporating recommendations from both the public and the SAB, a revised draft was transmitted to the SAB in May 1992 for a second review. Following a July 1992 public review meeting the

SAB panel endorsed the report and its conclusions, including a unanimous endorsement of the classification of environmental tobacco smoke as a Group A (known human) carcinogen.

The EPA also received and reviewed public comments on the second draft, and integrated all appropriate material into the final risk assessment. The final report was released in January 1993, at a joint press conference held by former Administrator Reilly and former Department of Health and Human Services Secretary Sullivan.

C. DIFFERENCES IN ANALYSIS, PROCESS, AND DOCUMENTATION BETWEEN THE EPA AND CRS REPORTS

As described above, the basis of EPA's conclusions on the human health effects of ETS is a total weight-of-evidence approach, which includes data on exposure, chemistry, animal and cell testing, as well as human studies on ETS, which provide the largest component. To support its findings that ETS is a "known human carcinogen", the EPA reviewed over 30 original studies on ETS and lung cancer, from eight different countries, and presented six major analyses of the dataset. The 530 page EPA report also presented over 100 original papers on the noncancer respiratory health effects of ETS. Together EPA's analyses of the human data alone on ETS health effects comprise well over 300 pages. This should be compared with the analysis in the CRS report which

1) references only 2 original papers on ETS and lung cancer and no original papers on the noncancer respiratory effects of ETS.

2) uses as its source material for critiquing the EPA report one position paper by the Tobacco Institute, and two papers published in Consumers' Research, a non-peer reviewed monthly magazine.

3) in a 5-page discussion on the health effects of ETS, primarily reiterates tobacco industry criticisms, most of which were aired at the open public reviews of the EPA report and were rejected by EPA's independent Science Advisory Board. There is no indication that the CRS conducted its own analysis of the evidence from the original sources.

4) is written by two economists, who by their own statement say, "Please note that we are trained as economists and our area of expertise relates to economic analysis and the associated areas of statistical inference and quantification of effects for purposes of cost-benefit analysis and related economic

policies. We do not have technical expertise in the physiological and biological transmission mechanisms of disease causing agents." (Statement of Dr. Jane G. Gravelle and Dr. Dennis Zimmerman, CRS, before The Subcommittee on Clean Air and Nuclear Regulation, Committee on Environment and Public Works, United States Senate, May 11, 1994)

5) has no stated peer review, compared with the EPA report, which was reviewed by a panel of 18 independent scientific experts in the field.

D. CRITIQUE OF THE CRS CRITICISMS OF THE EPA REPORT

Appendix A of the CRS Report (CRS-45 to CRS-49) contains several criticisms of EPA's report. These are responded to below.

1. The CRS report says that nonlinear relationships for health effects have been found for active smoking and cites page 44 of the Surgeon General's 1989 Report (CRS-45). This reference pertains to the British Physicians study (40,000 subjects) of active smoking and lung cancer. The CRS report ignores the dose-response relationship for lung cancer risk and number of cigarettes smoked per day from the much larger U.S. Veterans study (290,000 males) portrayed on the next page of the 1989 Surgeon General's Report, that suggests a linear relationship is quite reasonable. The data from another even larger U.S. study, the Cancer Prevention Study-I (previously American Cancer Society 25-State study; 840,000 subjects), are similarly consistent with a linear relationship, as are the data from many other studies of active smoking and lung cancer (See, for example, 1982 Surgeon General's Report, p.38). Furthermore, the CRS report does not cite any evidence for linear or nonlinear relationships for any health effects other than lung cancer.

2. The CRS report raises the question of how a passive smoking effect can be discerned from a group of 30 studies of which 6 are statistically significant (CRS-46 to CRS-47). This is an incomplete characterization of the total weight of evidence provided by these studies. For example, it overlooks the actual consistency of the study results. Twenty-four of the 30 studies found an increased risk of lung cancer in nonsmoking wives with smoking spouses compared to those with nonsmoking spouses. The fact that most did not achieve statistical significance is not surprising, because most of the studies had low statistical power to detect an effect, due to small sample sizes.

More importantly, these figures represent the data pertaining to an imprecise exposure measure--whether or not the spouse ever smoked. Spousal smoking is the most stable and sensitive single measure of ETS exposure; however, it is a crude measure because virtually everyone is exposed to ETS from a variety of sources. Therefore, women in the control group are not truly unexposed because they are exposed to ETS from sources other than spousal smoking. Furthermore, women in the exposed group are not all actually exposed to the largest relative exposures. Because of these "exposure misclassification" difficulties, the exposure differential between the control group and the exposed group is diluted, and the likelihood of being able to detect a relative effect is decreased.

To help overcome these difficulties it is important to look at what happens to the relative risks across exposure subgroups, for those studies that provide response data by exposure level, i.e. how much the spouse smoked. Comparing the high exposure groups to the control group provides a better exposure differential to determine whether or not there is an ETS effect. This is a standard practice in epidemiology. Seventeen of the 30 ETS and lung cancer studies provide information by exposure group; all 17 observed an increased risk in the highest exposure group. Nine of the 17 are statistically significant despite the further sample size reduction that occurs from subdividing the exposed group. Furthermore, all 14 studies that provide sufficient information for exposure-response trend tests show a positive exposure-response relationship, i.e. increasing risk with increasing exposure, and 10 of these are statistically significant.

The consistency of the results across the 30 studies, especially the high exposure group results and the dose-response relationships, provides compelling evidence that ETS is causally associated with lung cancer.

3. The CRS report implies that the EPA did something questionable in weighting the studies, "increasing the relative importance of studies with large sample size, studies that would tend to find more significant effects for passive smoking", and erroneously claims that the EPA "standardize[d] this diverse group of studies to account for statistically important differences in their methodologies" (CRS-47). In fact, the EPA, as one of its many analyses, combined the data for studies within countries. Studies between countries were not combined because of heterogeneity from country to country. Combining data from different studies provides an objective way to include data from both positive and nonpositive studies. The weighting procedure used, the inverse variance, is standard statistical

methodology. Furthermore, large studies are more likely to find statistically significant effects only if there is a true effect. If there were no association between ETS and lung cancer, the study size would be irrelevant.

4. The CRS points out that the EPA adjusted the results of each study for smoker misclassification bias (CRS-47). However, CRS did not clarify that smoker misclassification bias is the one known **upward** bias on the relative risk estimates, and that the adjustment has the effect of **decreasing** these estimates. The major source of bias, exposure misclassification, produces a downward bias on the relative risk estimates (see #3 above), and EPA did not adjust for this bias in making its carcinogenicity determination.

5. The CRS also emphasizes the fact that EPA used subjective judgments to "exclude" studies from its joint analysis (CRS-47). Again, the pooling of data was just one of the many analyses EPA conducted, and it was done both with and without tiering, which was based on explicit criteria. The results of the combined analysis, both with and without tiering, are consistent with the results of the analyses of the individual studies, and EPA's conclusion that ETS is a human lung carcinogen is not dependent on the combined analysis. Where a combined relative risk estimate is used for one of the quantitative analyses of the U.S. population risk, all of the U.S. studies are used.

6. The CRS says that the EPA changed "the standard for statistical significance from the usual standard, and the one generally used in the original studies" (CRS-47). The EPA used one-tailed 5% significance level tests to assess the results of the studies of ETS and lung cancer. This is a standard statistical technique when there is existing scientific evidence that, if there is an effect, it is likely to be in only one direction. Such is the case for lung cancer, because of the known carcinogenicity of active smoking and the chemical similarity between ETS and mainstream smoke. For the noncancer respiratory effects, where there was no such strong existing scientific evidence from active smoking, a two-tailed 5% significance level test was used. Furthermore, for the lung cancer studies, some of the original studies used one-tailed tests and some used two-tailed tests; when combining data, a single standard has to be used.

7. The CRS says that "the critical issue" is how large a chance we are willing to take that we accept the existence of a passive smoking effect when in fact one does not exist (CRS-48). The CRS description of the issue does not consider the consistency of the total evidence from the epidemiology studies (see #3), and the total weight-of-evidence as

described in Section A above. The 5% significance level used for the statistical testing reflects the probability of accepting an association from a single study when the association actually occurs by chance. The likelihood of the observed combination of results from the multiple studies of ETS and lung cancer occurring by chance is substantially lower. For example, the probability of 9 or more of 17 studies showing statistically significant associations for the highest exposure group by chance is less than 1-in-10-million. The probability of 10 or more of 14 studies showing statistically significant exposure-response relationships by chance is less than 1-in-a-billion.

8. The CRS report also suggests that different recollection of exposure by subjects with and without disease can bias the results (CRS-48). The results of the cohort studies, where exposure is ascertained before disease development, argues against such recall bias as being important in this case. Furthermore, the case-control study by Fontham et al.[1] used two different control groups, population controls and colon-cancer controls (who also have disease and, thus, may have different recall), to examine the issue of recall bias, and found no evidence of such bias.

9. The CRS report says that while EPA did make "some" adjustment for smoker misclassification, "it remains possible that a relationship observed might reflect the effects of active rather than passive smoking" (CRS-48). Again, the EPA did make an adjustment for smoker misclassification, and the procedure was specifically approved by the independent Science Advisory Board.

11. Similarly, the CRS acknowledges that the EPA "considered the presence of confounding factors in its evaluation of the studies", but says that "this issue is not laid to rest" (CRS-48). Hypothetical confounding is something that can never be fully ruled out; however, there is no evidence of such an effect for ETS and lung cancer. Several potential confounders were examined in the EPA risk assessment and were not found to affect the results. Furthermore, the epidemiology studies of lung cancer and ETS show consistent dose-response relationships in a variety of countries where diet and other lifestyle factors differ. There is no known factor that explains the consistent dose-response relationships observed in these diverse countries. For example, a high fat diet has been postulated as a

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[1] Fontham et al. (1991) Lung cancer in nonsmoking women: a multicenter case-control study. Cancer Epidemiol. Biomarkers Prev. 1:35-43.

confounding factor; however, the studies from Japan, where the diet is characteristically low in fat, show strong dose-response relationships for ETS and lung cancer. In addition, the study by Brownson et al. demonstrates lung cancer associations with both ETS[2] and dietary fat[3] in the highest exposure groups, yet finds no evidence that one factor confounds the other. The updated Fontham study[4] also examined a number of dietary and other potential confounders, and concluded that "the strong association in this study between adult ETS exposure and lung cancer risk cannot be attributed to any likely confounder"[4].

11. The CRS report says that two epidemiology studies that were published after the cutoff date for inclusion in the EPA report find no statistically significant increased lung cancer risk (CRS-48 to CRS-49). The CRS then says that both studies found a statistically significant increased risk in the highest exposure group, but that when large studies are "broken into several subsets and each is analyzed separately, some associations may be statistically significant by chance" (CRS-49). This comment does not reflect the consistency of the results for the highest exposure groups that the CRS notes two pages earlier (CRS-47). In addition, a third lung cancer study[5] that has come out since the EPA report, also showing an increased lung cancer risk in the highest exposure group. Including the 3 new studies and the update of the Fontham study[4], all 20 studies that provide data by exposure group find an increased lung cancer risk in the highest exposure group, and 13 of these are statistically significant, despite the small sample sizes.

12. The CRS report says that "many of the statistical concerns raised above with regard to lung cancer are relevant to respiratory effects in children" (CRS-49). However,

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[2] Brownson et al. (1992) Passive smoking and lung cancer in nonsmoking women. Am. J. Public Health 82:1525-1530.

[3] Alavanja et al. (1993) Saturated fat intake and lung cancer risk among nonsmoking women in Missouri. J. Natl. Cancer Inst. 85:1906-1916.

[4] Fontham et al. (1994) Environmental Tobacco Smoke and Lung Cancer in Nonsmoking Women: A Multicenter Study. JAMA 271:1752-1759.

[5] Liu et al. (1993) Indoor air pollution and lung cancer in Guangzhou, People's Republic of China. Am. J. Epidemiol. 137:145-154.

virtually none of the same concerns apply. i) The data on lower respiratory tract infections, for example, are even more consistent and show higher relative risk estimates than the lung cancer data. ii) Two-tailed significance tests were used for the noncancer effects. iii) Smoker misclassification is not an issue for infants and young children. iv) The noncancer studies were not pooled, so no issues of weighting or subjective tiering apply. v) Parental smoking is generally a very good surrogate of total ETS exposure in young children. vi) With acute effects, there is little concern for uncertain exposures in the distant past, so exposure recall is less of a problem. vii) Several noncancer studies[6] have biomarker evidence of ETS exposure, not just questionnaire data, and these biomarker data correlate with both the questionnaire data and the health effects, alleviating concerns about recall bias and about the validity of questionnaire data. viii) Studies that have come out since the EPA report are not just consistent with, but actually go further than, the EPA's conclusions pertaining to noncancer effects[7].

13. The CRS report raises the question of hypothetical confounding for the respiratory effects in children, saying that the "presence of other factors that may be related to these illnesses that are not controlled for are particularly important in the case of ... general respiratory illness, where the link between active smoking and disease is not as powerful as in the case of lung cancer" (CRS-49). The absence of a link between active smoking and respiratory effects in adults has little biological relevance to respiratory effects in children since young children represent a highly sensitive population because of their developing respiratory systems. As with lung cancer, the EPA did evaluate a number of potential confounding factors, and determined that they could not explain the observed associations. Furthermore, as with lung cancer, the consistent results observed across independent studies from

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[6] For example, Ehrlich et al. (1992) Childhood asthma and passive smoking: urinary cotinine as a biomarker of exposure. Am. Rev. Respir. Dis. 145:594-599; Etzel et al. (1992) Passive smoking and middle ear effusion among children in day care. Pediatrics 90:228-232; Reese et al. (1992) Relationship between urinary cotinine levels and diagnosis in children admitted to hospital. Am. Rev. Respi. Dis. 146:66-70; Chilmonczyk et al. (1993) Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. N. Engl. J. Med. 328:1665-1669.

[7] Schoendorf and Kiely (1992) Relationship of sudden infant death syndrome on maternal smoking during and after pregnancy. Pediatrics 90:905-908.

a variety of countries, with different lifestyle factors, argue against confounding.

E. EPA COMMENTS ON THE HEALTH EFFECTS COMPONENTS OF THE CRS ASSESSMENT OF COSTS DUE TO PASSIVE SMOKING

Our comments relate only to the CRS's assumptions pertaining to the health effects of passive smoking, and do not address the economic basis for the CRS analysis.

The CRS derives cost estimates using three different methods, each of which raises concerns, which are detailed below:

1. "Estimate based upon EPA's estimate of deaths from lung cancer" (CRS-11 to 12). In this case, the CRS multiplies the total costs per pack from active smoking by the ratio of lung cancer deaths attributed to passive smoking divided by the number attributed to active smoking. On the one hand, this overestimates the costs per pack from passive smoking, because some of the active smoking costs do not apply to passive smoking, for example, the costs from fires and medical expenditures associated with emphysema. On the other hand, if the CRS is trying to estimate the costs for all health effects that may be associated with passive smoking, a different ratio should be used. For example, Steenland, in the same article cited by the CRS (CRS-12 and CRS-46), estimates that 35,000 to 40,000 heart disease deaths per year in nonsmokers are attributable to passive smoking[8]. Combining heart disease and lung cancer, which at least represent the two major causes of smoking-attributable mortality, yields a ratio of about 0.13[9], which is roughly six times higher than the ratio used by the CRS. Furthermore, the costs for respiratory effects in children from passive smoking should be added, because these are effects whose costs are not reflected in the total costs from active smoking.

2. "Estimate based upon EPA's estimate of child hospitalizations" (CRS-12). Here, the CRS estimates the costs of hospitalizations for children suffering from ETS-

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[8] Since the EPA has not assessed the role of ETS in heart disease, we are neither endorsing nor disavowing these estimates; we merely suggest that they be included for consistency in the CRS methodology.

[9] 37,500 heart disease deaths plus 3,000 lung cancer deaths per year attributable to passive smoking, divided by 313,000, the number of heart disease and lung cancer deaths attributed to active smoking in 1988 [MMWR (1991) 40(4):63].

attributable lower respiratory tract infections. Other costs for respiratory effects in children resulting from passive smoking should be included, for example, hospitalizations for asthma attacks and for middle ear effusion, as well as costs of doctor visits and treatments for cases of lower respiratory tract infections, asthma, and middle ear effusion not requiring hospitalization.

3. "Estimate based upon relative physical exposure to smoke" (CRS-12). This method involves multiplying "the estimate of total active-smoking costs by the ratio of nonsmokers-to-smokers' physical exposure to smoke and by the ratio of nonsmoker to smokers" (CRS-12). The EPA believes that estimates of passive smoking effects based on "physical exposure to smoke" extrapolated from active smoking to passive smoking, rather than on the epidemiology data for passive smoking, are erroneous. There is no scientifically valid ratio of "physical exposure to smoke" between active and passive smokers. The CRS uses the ratio of urinary cotinine, but cotinine is a metabolite of nicotine, which is just one of over 4,000 compounds in tobacco smoke. Different compounds yield different ratios and are associated with different health effects. Nicotine, in particular, is known to underestimate exposures to many other ETS toxicants, because it adheres readily to materials in indoor environments and is therefore more rapidly removed from contaminated air than are other constituents. Thus, nicotine is similarly likely to underestimate health risks when extrapolating from active to passive smoking.

After adjusting for the "higher total active-smoking costs" estimated in the Manning study, the CRS states that its passive smoking cost estimates "seem rather high" and attempts to discount them (CRS-13). First, it states that "the epidemiological evidence for passive-smoking-related disease is weak" (CRS-13). The EPA strongly disagrees with this statement as noted above (See Sections A-D). Second, the CRS states that "the estimates based upon physical exposure assume a linear relationship between exposure and disease" and that nonlinear relationships for health effects have been found with respect to active smoking. As noted in #3 above, the EPA believes that the estimates based on physical exposure are unreliable because the concept of extrapolating "physical exposure to smoke" is flawed. Furthermore, as stated in #1 of Section D, the EPA disagrees with the statement that the relationships between exposure and health effects are "strongly nonlinear". The CRS cites as its basis page 44 of the Surgeon General's 1989 Report (CRS-13). This reference pertains to one British study of active smoking and lung cancer. The CRS report cites no evidence for nonlinear dose-response relationships for any other health effects and does not address data from the many other studies of lung cancer and active smoking, including data from a much larger U.S. study that appear on the next page of the Surgeon General's Report, that suggest a linear relationship is reasonable.

ATTACHMENT 8

The Costs and Benefits of Smoking Restrictions

An Assessment of the Smoke-Free Environment Act of 1993 (H.R. 3434)

Prepared at the request of:

Congressman Henry Waxman
Chairman, Subcommittee on Health and The Environment
Committee on Energy and Commerce
U.S. House of Representatives

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April 1994

The Costs and Benefits of Smoking Restrictions

An Assessment of the Smoke-Free Environment Act of 1993
(H.R. 3434)

Executive Summary

Introduction

In August 1993, H.R. 3434, the Smoke-Free Environment Act of 1993, was introduced in the House of Representatives by Congressman Henry Waxman (Chairman of the Subcommittee on Health and the Environment of the Committee on Energy and Commerce) with more than 40 co-sponsors. This Bill would require that all nonresidential buildings regularly entered by 10 or more persons in the course of a week adopt a policy that bans smoking inside the building or restricts it to separately ventilated and exhausted smoking rooms. The Bill would allow enforcement actions in the United States District Courts by an individual, government, or other aggrieved entity, with allowable fines of up to $5,000 per day.

H.R. 3434 would effectively ban or restrict smoking in most indoor environments. As written, these environments would include such diverse establishments as office buildings, schools and other educational establishments, theaters, restaurants, hotels, hospitals and other health care facilities, sports arenas, retail establishments, and manufacturing plants.

In a recent letter to Carol Browner, Administrator of the United States Environmental Protection Agency (EPA), Congressman Waxman requested that EPA analyze (quantitatively where possible) the compliance costs and the health and economic benefits of H.R. 3434. Specifically, he asked that EPA assess the cost of compliance including provisions for smoking lounges; the value of benefits resulting from reduced exposure to environmental tobacco smoke and changes in smoking behavior; the value of increased productivity and reduced absenteeism; savings from reduced operation and maintenance costs; and savings in fire related injuries and property damage.

Role and Limits of Cost-Benefit Analysis

In principle, cost-benefit analysis can be a useful tool for helping to identify those government actions which leave society as a whole better off. It can contribute to such assessments by providing a systematic framework for measuring and comparing the net economic benefits of policy alternatives. Cost-benefit analysis does not by itself, however, provide definitive answers regarding the merits of public health and environmental policy alternatives. Rather, net benefit estimates must be combined with other information, and weighed with other policy considerations, to formulate effective public policy. Pursuant to this, and consistent with Executive Order 12866, EPA routinely weighs the full range of relevant policy considerations, such as distributional effects, legal issues, and institutional issues in making regulatory decisions. In keeping with this approach, EPA presents the current analysis, which the Agency believes provides useful insights regarding many of the potential costs and benefits of H.R. 3434.

converted to equivalent annual values using a 3% social discount rate. Sensitivity analyses using 5% and 7% discount rates are also provided.

Throughout this analysis it is assumed that H.R. 3434 would apply to all the previously stated buildings, at all times, without exception. It is also assumed that full compliance would be achieved within the first year of implementation.

Choice of Baseline for Assessing Costs and Benefits

Per capita cigarette consumption has been steadily falling over the past several years. In addition, recent survey data suggest that many establishments already have some form of smoking policy, and the percent of establishments which report having such policies has been increasing in the past few years (DHHS, 1992; BNA 1991). Therefore, it was necessary to establish a baseline from which to measure the effects of H.R. 3434 from enactment forward. This was accomplished by a three step procedure.

In the first step, the net costs and benefits are computed assuming current cigarette consumption levels, and assuming that there are currently no restrictions. This is an artificial baseline used for analytic convenience, but may be interpreted as a reflection of the cost and benefit differences in a society with and without smoking restrictions comparable to H.R. 3434.

Second, survey data were examined concerning the prevalence of smoking policies already in place, and using assumptions about the nature of those policies as well as policies in small establishments not covered in those surveys, an estimate was derived that 23% of the population is covered by smoking restrictions comparable to the requirements of H.R. 3434. Current cigarette consumption levels, and 23% coverage by existing policies are therefore used as the baseline for this study. As a result, this study concludes that 23% of the previously calculated cost and benefits are attributable to existing policies, and 77% are attributable to H.R. 3434, or other future restriction policies, including private initiatives.[1]

Finally, sensitivity analyses to the baseline assumptions are conducted by calculating the changes to the costs and benefits that would result from alternative assumptions about future trends. The specific variables tested include future trends in cigarette consumption, and future trends in the development of public and private smoking restriction policies which could take place in the absence of national legislation. These alternative scenarios of potential future trends are intended to demonstrate how the absolute levels of incremental costs and benefits attributable to H.R. 3434 are sensitive to assumptions about the future prevalence of smoking restrictions enacted by other public and private entities, and to future trends in cigarette consumption.

Other Economic Impacts

Economic considerations which legislators may wish to consider go beyond just costs and benefits assessed in this analysis. Where information from this analysis sheds light on some of these considerations, they are briefly described.

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[1] As this report was being prepared, the President signed into law the Goals 2000: Educate America Act. This legislation restricts smoking in all federally funded primary and secondary schools and in day care centers. Because a sensitivity analysis is presented of the alternative baseline assumptions, no specific adjustments to account for this new law were made to the 23% baseline calculations used to assess the effect of H.R. 3434.

operations used by state governments would cost between $0.1 billion and $0.2 billion per year. Recognizing that these two issues are not strictly comparable, an estimate of between $0.1 billion and $0.5 billion per year appears plausible for a society with no current restrictions, and is used in this analysis. This would translate into an estimated enforcement cost of between $0.1 billion and $0.4 billion per year under current baseline (23% coverage) conditions. Some expenditures by the Federal government and by state and local governments can be expected for information dissemination, though they may well be less than the value of current resources devoted to passing controversial state and local legislation.[4] These expenditures were not quantified.

The Effects of Reduced ETS Exposure

The Health Consequences of ETS

A major component of the benefits that could be achieved from national legislation that restricts smoking in public places is from reduced exposure of building occupants to ETS.

Exhibits ES-2a and ES-2b present information on the health consequences of ETS. For the purpose of valuing the benefits resulting from reduced exposure to ETS due to smoking restrictions, several conservative adjustments to these figures were made. First, all deaths and illnesses associated with maternal smoking were excluded because the primary route of exposure is not expected to be through ETS in public buildings.[5] Therefore, the deaths associated with spontaneous abortions, sudden infant death syndrome, respiratory conditions in newborns, and short gestation/low birth weight newborns were also excluded, as were the morbidity consequences of low birth weight and neonatal intensive care.

The second conservative adjustment relates to heart disease. The American Heart Association estimates that between 35,000 and 40,000 heart disease deaths occur every year because of ETS (Taylor, 1992). This is based on studies in which estimates of the effect of ETS on heart disease fall in the range of 32,000 to 40,000 deaths per year as presented in Exhibit ES-2a. Because these estimates are substantial, and because EPA did not formally assess heart disease risks in its ETS risk assessment (EPA, 1992), two conservative adjustments to these figures were made.

- First, the low end of the range (32,000) was used as the high estimate, and this was reduced by 50% (16,000) to obtain the low estimate.

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[4] Even when smoking restrictions are passed at the state or local level, campaigns to nullify the legislation or to preempt local legislation with weaker state legislation can involve the expenditure of significant resources on both sides of the issue. No attempt was made to quantify current costs to state and local entities, though national legislation would be expected to reduce many of these costs. For an excellent analysis of this issue as it is manifested in California, see Macdonald and Glantz (1994).

[5] While the primary route of exposure is maternal smoking, it is estimated that smoking restrictions comparable to H.R. 3434 would reduce the size of the smoking population because some smokers would quit, and some future smokers would refrain from initiating the habit. In addition, it is estimated that the rate of consumption of remaining smokers would be reduced. To the extent that these changes in behavior will affect maternal smoking, some reductions in these excluded effects would also likely occur, resulting in benefits. The current study did not, however, quantify these potential benefits in our calculations.

benefits from reduced asthma induction, a willingness to pay measure associated with chronic bronchitis,[10] which is also a chronic respiratory disease was used.

The total benefit from reduced ETS exposure includes both the benefits of premature deaths avoided plus the benefits of reduced illness. The total benefits due to reduced ETS exposure is thus estimated to be $35 billion to $66 billion per year.

Increased Comfort of Building Occupants

This analysis assumes that, all else being equal, no building occupant would prefer being exposed to environmental tobacco smoke, and that most derive benefits from a smoke free environment. With the exception of the health, productivity, and safety effects discussed elsewhere, these benefits are largely intangible, and include such factors as reduced irritation and reduced environmental odor, and less annoyance with tobacco smoke residuals left on hair and clothing. These effects are more bothersome to some than others, but may be of considerable importance to some persons.[11] In the present study, no attempt was made to quantify these benefits. However, because the overall results do not include the benefits of increased comfort, and because of the pervasive use of conservative assumptions in this analysis, it is expected that the estimate of total benefits from reduced ETS exposure is conservative.

Savings in the Operation and Maintenance of Buildings

Smoking in a building involves implicit operational and maintenance expenses. In addition to emptying and cleaning ashtrays, the smoke, ashes, and accidental burns on furniture and carpets create an additional housekeeping and general maintenance burden. For example, the Building Owners and Managers Association (BOMA) International reports that in a tightly monitored program, a member firm experienced a 15% reduction in housekeeping costs when a non-smoking policy was introduced. Maintenance costs were not covered in the monitoring program. Changes that were observed included elimination of the need to empty or clean ashtrays; reduction in high surface dusting and the dusting of desks and tabletops; reduced detailed vacuuming around desks of smokers; and reductions in the cleaning of venetian blinds and heating, ventilation, and air conditioning (HVAC) vents. In addition, cleaning personnel found that they spent less time moving articles on desks in order to remove ashes. BOMA cautions that this was a tightly monitored program, and that actual experience may only produce an average of 10 % in overall cleaning costs.[12] Maintenance cost savings include less frequent replacement of furniture, reduced cost of carpet repair , savings in the repair of computer equipment operated by smokers, and sometimes less frequent painting.

The actual savings in both housekeeping and maintenance expenses are expected to vary from building to building depending upon use (e.g., offices versus retail stores). A separate estimate was therefore developed for different uses: offices, mercantile and services (retail), food service, health care, assembly, education, lodging, and warehouse/industry. The cost effectively. Second, in order to smoke, smokers would have to leave the work station and go either to a designated smoking lounge or outside to smoke. The resulting effect on productivity would be limited because taking occasional breaks is already a normal part of the workday for most persons. Thus, while it is likely that some decrement in productivity would result from these two effects, it is not likely to be large relative to the productivity gains from reduced ETS exposure, and it would be difficult to quantify.

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[10] Based on willingness to pay measure for reducing the incidence of chronic bronchitis (Neumann. et al. 1994), the estimated value of avoiding chronic asthma is assumed to be $1.5 million per case.

[11] See for example letters to the editor in the Journal of the Medical Association of Georgia, Vol. 79, March 1990, page 273.

[12] Personal correspondence from James Dinegar, BOMA International to David Mudarri, EPA. January 1994.

Net Effect on Productivity

There are both positive and negative influences on productivity. The ETS effect would *increase* productivity and apply to all employees. However, some smokers would work less effectively and some would spend more time going to and from an allowable smoking area. This may *decrease* productivity, but would apply only to smokers, and only to some portion of the smoking population. Quantitative estimates of these effects could not be developed for this study.

Benefits from Reduced Absenteeism

In addition to considerations of on-the-job productivity, smoking restrictions would yield productivity gains by reducing absenteeism. After accounting for differences in socioeconomic characteristics between smokers and persons who have never smoked, smokers are estimated to have about 50% more workdays lost than persons who have never smoked, and former smokers are estimated to have about 30% more workdays lost than never smokers (Manning. et al. 1991).

There is a plausible presumption that an institutional environment that restricts smoking and that supports abstinence will reduce cigarette consumption among smokers, increase attempts to quit and quitting success rates, and reduce the rates at which nonsmokers take up smoking. However, in 1989, the Surgeon General found that evidence of the effect of smoking restrictions on actual smoking behavior was considered to be inconclusive (DHHS, 1989). Since that time, a number of studies appear to support the conclusion that such restrictions have some of the postulated effects on smoking behavior (see Appendix A).

Based on a review of these recent studies, it is estimated that between 3% and 6% of current smokers would quit as a result of national legislation that restricts smoking. This would result in an immediate decrease in the number of smokers and an equivalent increase in former smokers. We also estimate that the initiation rate for new smokers would decrease by 5% to 10%. This would ultimately result in an equivalent proportional reduction in the number of smokers, and an equivalent absolute increase in the number of persons who have never smoked. However, the effect of the reduced initiation rate would occur gradually over a 50 to 60 year period. The average daily earnings including fringe benefits of smokers is about $104, and discounting all future effects by 3% yields an estimated savings of under $0.5 billion per year. This is quite insignificant when compared with other effects.

Savings in Smoking-Related Fires

Most smoking-related fire injuries and property losses are in residential environments, which would not be subject to smoking restrictions. For example, between 1988 and 1990, there was an annual average of some 1,328 smoking related fire fatalities in residences compared to an annual average of 38 fatalities in nonresidential buildings (Miller, 1993). Likewise, property damage due to smoking-related fires over the same period averaged some $316 million annually therefore inappropriately omit the value of all these other costs and benefits to smokers, resulting in potentially biased measures of the welfare change to society.

Second, analysts disagree whether the traditional economic models one might use to measure the welfare change to smokers can be reasonably applied, particularly given limits on available data. To obtain reasonable estimates of the change in net benefits to smokers, these traditional models require that the subjects -- smokers in this case -- are acting rationally in response to a free and open marketplace. Furthermore, these consumption decisions must either be devoid of significant price distortions such as taxes and subsidies, or analytical corrections must be made to take account of these distortions. With respect to the rationality requirement, questions have been raised whether the rational consumer choice model applies given the apparent addictive nature of smoking, or to the delicate question of smoking initiation by teenagers.[18] Questions have also been raised whether the consequences of taxes (e.g., cigarette tax) and subsidies (e.g., tobacco farm subsidies, subsidized health care) significantly distort consumer decision-making in this case.

Third, EPA is concerned that currently available data are insufficient to support using a traditional economic model to estimate the change in net benefit to smokers caused by H.R. 3434. The reason for this is H.R. 3434 does not prohibit smoking outright, nor does it change the purchase price or quantity of cigarettes available. Instead, H.R. 3434 only compels changes in the location and/or time pattern of cigarette consumption. This would be expressed in economic terms as an increase in the transaction cost of smoking, and the transaction cost would vary widely among smokers. Since it is unclear how the slope of the demand curve for cigarettes might shift in response to a nonuniform increase in transaction costs to smokers, a reliable measure of the change in net benefits to smokers cannot be decided.

Based on the foregoing, this study makes no attempt at this time to quantify the economic value of the consequences of H.R. 3434 to smokers themselves.

Comparing Costs and Benefits

While several elements of costs and benefits were not quantified, and bearing in mind the limitations presented by the current analysis, two principal findings emerge. First, it is clear that the benefits of smoking restrictions comparable to H.R. 3434 substantially outweigh the costs for those items quantified in our analysis. Second, comparing the high estimate of costs with the low estimate of benefits does not change the fundamental conclusions that benefits significantly exceed costs.

It should be noted that no attempt was made in the current analysis to evaluate the costs and benefits of altering provisions of the legislation. Throughout the analysis, no exception in scope or timing of the provisions of H.R. 3434 were assumed. Clearly, changing provisions such as the scope or timing of the restrictions would affect both costs and benefits.

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[18] Note, however, that some analysts subscribe to models of "rational addiction" which have been developed and empirically tested (Becker and Murphy,1988);(Chaloupka,1991). However, these models do not take account of those who underestimate the strength of the addiction, or, who, for whatever reason, fail to appreciate the magnitude of the adverse consequences.

Nor do the models appropriately confront the difficult question of the consequences from teenage smoking. These models demonstrate that teenagers tend to disregard the future consequences of smoking more so than do adults (Chaloupka, 1991). Reducing teenage smoking is generally regarded as a benefit, and legislation in most States prohibits the sale of tobacco products to teenagers.

Other Economic Considerations

The estimates of costs and benefits covered in this analysis are a subset of potential economic consequences that policy makers may wish to consider.

Restoration of Lost Income

Implementing smoking restrictive legislation nationally would result in the restoration of approximately $31,000[19] for each pre-retirement year of premature death which is avoided because of smokers who quit, cut back, or fail to become smokers because of H.R. 3434. On average, we estimate that each premature death avoided because of quitting and reduced consumption would add approximately 1.4 to 4 salary earning years, and each premature death avoided from persons who refrain from becoming smokers would add approximately 11 salary earning years of life.[20] When future values are discounted at 3%, this analysis estimates that between $3 billion and $6 billion of lost income would be restored. A similar estimate was not possible for persons exposed to ETS, though this effect should be considered. The importance of this impact is enhanced to the extent that some children, spouses, the elderly or disabled may be dependent on such income.

Reduced Burden on the Medical Service Industry

Every year, the average expenditure for medical services for smokers and former smokers exceeds that of nonsmokers. However, this is partially offset by the fact that nonsmokers live longer, and continue to consume medical services during the extra years of life. When both of these factors are taken into account, the result is a net excess burden on the medical service industry of about $35 billion per year due to smoking.[21] Assuming that changes in the excess medical expenditures due to smoking restrictions would be proportional to changes smoking related premature deaths, this analysis estimates that every reduction in annual premature death would represent an annual reduction of $85,000 for medical services. Accordingly, when future savings are discounted at 3%, H.R. 3434 would reduce annual expenditures for medical services by $2.3 billion to $4.7 billion per year. It is not clear from our analysis what net impact reduced exposure to ETS would have on the medical service industry.

Potential Cost to Social Security and other Pension Funds

Persons who would otherwise have died prematurely would live longer under smoking restrictions and collect pensions and social security during those extended years. Each premature death avoided for smokers who quit, cut back, or fail to initiate smoking represents an extension of life of about 5 to 7 years beyond the age of 65, during which time they would be eligible to collect a pension annuity. Data are not currently available to support a similar estimate for ETS exposed individuals.

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[19] The estimated annual earnings of smokers is inflated by 20% to account for earnings after the age of 65, based on OTA (1993).

[20] Salary earning years are assumed to be years prior to the age of 65.

[21] This is estimated from information provided by Hodgson (1992) who compares excess medical costs over the lifetime of persons who have ever smoked , and persons who have never smoked. Similar data and procedures were also used by Manning. et al. (1991).

Assessment of Costs and Benefits In A Society With No Smoking Restrictions

In this section,the costs and benefits associated with smoking restrictions are assessed from a hypothetical baseline in which we assume that no restrictions in the public or private sector are currently in place. The results in this section may be interpreted as measuring the cost and benefit differences between a society with smoking restrictions versus a society without such restrictions. After completing the analysis using this hypothetical baseline, the costs and benefits of H.R. 3434 are assessed under estimates of current baseline conditions, and the sensitivity of these results is evaluated using alternative baseline assumptions.

Section 1. Cost of Implementing Smoking Restrictions

Cost of Implementing Smoking Bans

Despite the apparent wide use of some forms of smoking restrictions, there are no published data on the cost of compliance. While many establishments have smoking policies, it is not common for them to develop compliance cost information. Some preliminary data on compliance costs for worksites may be published soon as part of the Community Intervention Trial (COMMIT) project sponsored by the National Cancer Institute (Lewit, 1993). In the absence of specific data, estimates are developed for start-up costs which would occur initially, and for recurrent costs associated with maintaining the policy once it was established.

In establishing smoking bans nationally, responsible entities would incur initial costs to develop the policy, assign responsibilities, print and distribute information, print and post signs, remove ashtrays and cigarette vending machines, provide outdoor receptacles, and develop compliance procedures. Initial costs include a one time increase in participation in smoking cessation programs. Subsequent to these initial start-up costs, establishments will incur annual costs for policy maintenance. The estimates used in this analysis are provided in Exhibit 1-1. For simplicity, the estimates were developed for a prototype company with 1,000 employees.

According to Bureau of Labor Statistics (BLS) data, in 1990 there were approximately 118 million people in the employed civilian labor force (excludes military). Subtracting approximately 8 million for those who work in farming and the construction trades leaves 110 million persons employed indoors. The 110 million figure is used as the basis for calculating national costs of implementing smoking bans nationally.

The national cost estimate is presented in Exhibit 1-2. Initial costs are annualized in two ways. First, all the initial costs will be experienced in the first year or so that the policy is initiated. The annual equivalent of that initial cost is the interest cost at the appropriate interest rate.[2] In our analysis, we use a 3% social discount rate for our calculations. Second, the initial costs will recur when new establishments are formed. We assume a 15% turnover rate every year, so that 15% of the initial cost will be experienced every year by these new establishments.[3]

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[2] Since the relevant quantity is the equivalent annual cost that would occur every year, in perpetuity, this is equivalent to borrowing the money and paying interest but no principal every year.

[3] An establishment here is any new business, as distinguished from a new building. It is assumed that any new establishment would experience the initial costs of establishing a policy.

Outdoor Shelters with Smoking Bans

A few firms that have thus far established smoking bans now provide some form of outdoor smoking shelter for smoking employees. We assume that 10% of firms that ban smoking will provide this feature, so we included an estimate in our calculations.

A 9' x 12' free standing shelter (similar to a bus shelter) of aluminum frame with acrylic glazing would cost about $4,800 or $44 per square foot (Means,1991). Less elaborate structures, such as a bench under available shelter would cost considerably less. The cost of outdoor shelters is assumed to be, on average, about the same as the cost of indoor shelters, or about $25 per square foot. Maintenance costs are included in the cost of establishing a smoking ban.

Costs of Smoking Lounges

Smoking Lounge Requirements

H.R. 3434 requires that specifically designated smoking lounges meet appropriate standards for ventilation. To be properly ventilated, a smoking lounge should meet the following requirements (EPA 1993, ASHRAE 1989).

- Air from the smoking lounge should be directly exhausted to the outside by an exhaust fan. Air from the smoking lounge should not be recirculated to other parts of the building. This may require that the plenum (the space between the ceiling tiles and the next floor) be sealed and isolated from the remainder of the building.

- More air should be exhausted from the lounge than is supplied at all times. This insures that the area is under negative pressure, so that smoke does not drift to surrounding spaces.

- The ventilation system should provide the smoking room with 60 cubic feet per minute (cfm) of supply air per smoker. Smoker densities of 7 persons per 100 square feet are often assumed. This air may be supplied by air transferred from other parts of the building such as corridors.

- Nonsmokers should not have to enter the smoking room for any purpose.

Construction of separately ventilated lounges in existing buildings may require modification of the building ventilation system to isolate return air and establish the exhaust system. Because of the requirement that air be exhausted directly to the outside, rooms with an outside wall or on the top floor are preferred. On the outside, exhaust vents must be adequately separated from the air intake vents which supply outside air to the building's ventilation system. The exhaust air may have to be filtered to avoid soiling on windows and on the outside surface.

There are three options for supplying ventilation air to the smoking area. The first is to transfer air from surrounding spaces. This may enter through grills in the door or through a separately constructed supply duct. The second option is to supply air from the main ventilation system, and the third option is to provide a dedicated supply air system for the smoking area. The first option is the cheapest but also the most susceptible to creating ventilation imbalances that compromise the integrity of the building's ventilation system and may generate complaints. The second option requires that the ventilation system have sufficient capacity to satisfy the supply air requirement for the room and still meet the demands of the rest of the system. While most systems are built with excess capacity, a recent increase in ASHRAE requirements for outdoor ventilation (ASHRAE 1989), or higher than designed occupant densities, may reduce that excess. The last option is the most expensive, but will offer the best guarantee that the system operates without complaint.

Number and Size of Lounges

It remains to estimate the lounge area that would normally be supplied to satisfy the smoking population in those establishments that choose this option. There are no published guides to help make this estimate. Therefore, the analysis derives an estimate by formulating an example of a site with 100 smokers. Each smoker is assumed to smoke before work and during lunch which will be outside of the building, and will take a 15 minute break once in the morning and once in the afternoon. Each break will take 3 minutes in transit, and 12 minutes in the smoking lounge. Smokers will visit the lounge over a two hour period, averaging 50 smokers an hour. If evenly distributed over the hour, there would be 10 smokers in the lounge all the time. Assuming a 50 percent variance for peak use gives an estimate of 15 smokers in peak use. Smoking lounges may be designed for 7 smokers per 100 square feet (ASHRAE 1989). This means that about 200 square feet of smoking lounge would be needed to satisfy a peak demand of 15 smokers. The design parameter then is to build 200 square feet of smoking lounge for every 100 smokers to be accommodated, or 2 square feet of lounge per smoking occupant. Exhibit 1-3 provides an estimate of the lounge construction requirements.

Each smoker may count as a smoking occupant in different buildings. For example, a smoker spends some time at work, some time in a restaurant, in a sports facility, etc. Therefore, the number of potential smoking occupants rather than numbers of smokers is a better measure for estimating the number of smoking lounges that may be built. In 1990, there were approximately 46 million smokers in the United States, and about 65% of the adult population was employed. Assuming the same employment rate for smokers would give us an employed smoking population of about 30 million persons who are the smoking occupants for the nation's workplaces. In addition, there were approximately 117 million seat or bed accommodations in educational facilities, restaurant facilities and hospitals (DOE 1991). Assuming a capacity utilization rate of 80%, gives us approximately 100 million accommodations, of which 25% (25 million) will be used by smokers (About 25% of the population are smokers.). Thus, the total smoking occupant base for our calculations is taken to be 30 million plus 25 million or 55 million smoking occupants.

Cost of Construction and Maintenance of Smoking Lounges

A significant cost element for smoking areas inside buildings is the potential cost of ductwork. Since the area must be exhausted directly to the outside, rooms in the interior portion of the building will require horizontal and/or vertical ducts. Vertical ducts would be used to carry exhaust air from lower floors to the roof of the building through the central core of the building. Horizontal ducts would be used to reach the central core, or to exhaust the air through an outside wall. The building structure can make vertical duct construction prohibitive in existing buildings. Exhausting through the exterior wall can create films of exhaust materials on windows unless the exhaust air is properly filtered, or the exhaust air may infiltrate back into the building under certain conditions.

The Building Owners and Managers Association International (BOMA) reports that retrofitting ventilation systems to accommodate smoking room ventilation requirements is very costly, if not impossible in some cases. In new buildings, the design and installation of separate ventilation systems is reported to cost $30 - $50 per square foot (Hurwitz 1993).

Based on conversations with Digital Equipment Corporation and Connecticut Mutual Life Insurance, Environmental Health & Engineering (EH&E) (1992) suggests that lounges cost on the order of $40 - $50 per square foot, but could be as low as $20 per square foot if the room is already adequately enclosed, furnishings exist, and the room can be exhausted to a nearby exterior wall with minimum difficulty.

A firm in Dallas, Texas has made a business of providing smoking lounges to commercial establishments (Poynter 1993). The firm avoids vertical ducts, filters the exhaust air to avoid filming on windows, and provides a service contract to building owners which allows them to pass on the expense to tenants. According to its advertising literature, the firm would charge approximately $30 per square foot up-front costs plus an annual cost of about $25 per square foot to completely maintain the space and the ventilation equipment. This includes the rental fee for the space.

National Cost of Compliance under the Smoking Lounge Option

The Poynter 1993 estimate for indoor lounges is somewhat lower than the other estimates. However, it falls within the EH&E range, and is based on real market experience. Further, it is reasonable to assume that the indoor smoking lounge option will be used only when the costs are sufficiently low to make this option attractive. The Poynter estimate is used to calculate compliance cost. It is then increased by 30% to provide a high estimate. Calculations are provided in Exhibit 1-4. An initial average cost of $25 per square foot would be experienced by all establishments that choose to provide interior smoking lounges to accommodate smokers. This is translated into an annual equivalent cost using a 3% discount rate, to which is added a recurrent portion which would be experienced when old structures are torn down and new ones built. We assume an average life of 20 years (or a turnover rate of 5% per year), so that 5% of this cost would recur annually.

The total annual cost estimates represent the national cost if every establishment elected to comply with smoking restriction requirements using the smoking lounge option.

Proportion of Establishments Which May Choose to Provide Smoking Lounges

Once fully implemented, only 10% (low estimate) to 20% (high estimate) of employees are expected to be serviced by smoking lounges (see Exhibit 7-3b for justification of this assumption). There are several reasons that most entities are not expected to provide a smoking lounge.

- Smoking lounges would have to meet stringent ventilation requirements and could not be spaces in which nonsmokers would have reason to enter. Most existing rooms with available outside exhaust such as rest rooms would not be allowed.

- Smoking lounges are more expensive and more complicated than smoking bans. It is likely that smoking lounges will be chosen only when they are relatively inexpensive and convenient.

- Smoking lounges may require exceptional diligence to insure that exhaust is adequate, that the space is under negative pressure, and that the building's ventilation system is balanced. Smoking lounges are generally associated with greater complaints and with lower reported satisfaction with the smoking policy than smoking bans, and smoking bans are becoming increasingly popular (Sorensen. et al. 1991, 1991a, 1992; Stillman. et al. 1992)

- Smoking lounges compete for space with other potential uses and could result in foregone rental revenue.

Enforcement

Costs to building owners for ensuring compliance in their building is included in the cost of implementing smoking bans. With respect to enforcement by governmental jurisdictions, H.R. 3434 provides no specific requirements for enforcement of its provisions, other than through citizen suits in Federal court. Therefore, enforcement costs are difficult to quantify. Some expenditures by the Federal government and by state and local governments can be expected for information dissemination, though they may well be less than the value of current resources devoted to passing controversial state and local legislation.[4] These expenditures were not quantified. Information dissemination on a uniform requirement at a national level would likely enjoy greater efficiencies, and some reductions in resources currently devoted to passing and maintaining controversial state and local legislation, and in litigating private sector policies, would likely occur.

In a proposed rule concerning the sale or distribution of tobacco products to individuals under eighteen years of age, the Department of Health and Human Services [5] estimated that sting-type operations used by state governments would cost between $0.1 billion and $0.2 billion per year. Recognizing that these two issues are not strictly comparable, an estimate of between $0.1 billion and $0.5 billion per year appears plausible, and is used in this analysis as the cost of enforcement in a society with no current compliance with standards comparable to H. R. 3434. *(See Exhibit S-2 for estimates of H.R. 3434 under current baseline conditions.)*

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[4] Even when smoking restrictions are passed at the state or local level, campaigns to nullify the legislation or to preempt local legislation with weaker state legislation can involve the expenditure of significant resources on both sides of the issue. No attempt was made to quantify current costs to state and local entities, though national legislation would be expected to reduce many of these costs. For an excellent analysis of this issue as it is manifested in California, see Macdonald and Glantz (1994).

[5] Department of Health and Human Services, Substance Abuse and Mental Health Administration, 45 CFR Part 96, Substance Abuse Prevention and Treatment Block Grants: Sale or Distribution of Tobacco Products to Individuals Under 18 Years of Age: Proposed Rule.

Section 4. Increased Productivity and Decreased Absenteeism Resulting from Smoking Restrictions

Effects on Productivity

On-the-Job Productivity Improvements from Reduced ETS. It is generally agreed that exposure to ETS reduces the productivity of "individual" building occupants, probably more for nonsmokers than smokers, though no reliable basis for quantifying this effect could be found. It is also likely that clearly defined and fairly implemented smoking policies will increase "organizational" productivity by reducing potential conflicts between smokers and nonsmokers. Evidence suggests that well-run smoking restrictions are popular among both employees and management, and that when they are well managed and tailored to the social norms of individual worksites, they are effective (Andrews. 1983; Hocking. et al. 1991; Hudzinski, 1990; Peterson. et al. 1988; Sorensen. et al. 1986; Sorensen. et al. 1991; Stave. et al. 1991). Nevertheless, no basis for quantifying effects on organizational productivity could be found.

Losses in Productivity from Restrictions to Smokers. While reduced ETS exposure would likely have some positive impact on smokers' productivity, the inability to smoke at their workstations would likely have the opposite effect. This could occur for two reasons. First, depending on their level of addiction, some smokers who want to smoke, but are restricted, may become uncomfortable, and less able to work effectively. Second, in order to smoke, smokers would have to leave the workstation and go either to a designated smoking lounge or outside to smoke. The resulting effect on productivity would be limited because taking occasional breaks is already a normal part of the workday for most persons. Thus, while it is likely that some decrement in productivity would result from these two effects, it is not likely to be large relative to the productivity gains from reduced ETS exposure, and it would be difficult to quantify.

Net Effect on Productivity. There are both positive and negative influences on productivity. The ETS effect would *increase* productivity and apply to all employees. However, some smokers would work less effectively and some would spend more time going to and from an allowable smoking area. This may *decrease* productivity, but would apply only to smokers, and only to some portion of the smoking population. Quantitative estimates of these effects could not be developed for this study.

Benefits from Reduced Absenteeism

Several studies suggest that smokers have a greater number of sick leave absences from work than nonsmokers or former smokers. Using data from the 1979 Report of the Surgeon General which estimated that 81 million working days were lost to smoking, and dividing by the number of smokers, Kristein (1983) estimated the excess days lost due to smokers to be 2 days per year. Rice. et al. (1986) presents data from the supplement to the 1979 National Health Interview Survey showing an average of 4.9 work-loss days per employed person per year. Non-smokers average 4.3 work-loss days while current smokers and former smokers combined average 5.4 work-loss days (or 25% more than non-smokers). Jackson. et al. (1989) also report on other studies which showed 1.5 - 2.2 excess workdays lost per month for smokers compared with ex-smokers. Unpublished data from the 1991 National Health Interview Survey show a difference in the reported mean days lost of 1 day between smokers and former smokers, and 1.7 days between smokers and never smokers.

The difficulty in making direct comparisons between the absentee rates of smokers and nonsmokers is that smokers are generally less educated, have lower incomes, are more likely to be in blue collar jobs, and are more likely to be alcohol users. These factors could account for some or all of the differences. However, recent evidence suggests otherwise. Reporting on a study of an eastern North Carolina pharmaceutical company, and using a time-series control group design, Jackson. et al. (1989) report a significant difference between current smokers and ex-smokers, and between smokers before and after cessation. Likewise, Manning. et al. (1991) examined data from the 1983 National Health Interview Survey and concludes that after controlling for age, sex, race, and education, former smokers had 31% more work-loss days and current smokers had 52% more work days lost per year than never smokers.

The 1993 NHIS data show a mean value in days lost from work of 3 days for never smokers. We will use Manning. et al.'s results to compute days lost for smokers and former smokers since they controlled for confounding variables. Thus, there are associated 0.9 (3 x .31) absentee days per year saved for each smoker who has quit and 1.5 (3 x .52) absentee days per year for each potential smoker who has refrained from becoming a smoker. Results are shown in Exhibit 4-1.

In Section 6 below, it is estimated that between 3% and 6% of current smokers would quit as a result of national legislation that restricts smoking, resulting in an immediate decrease in the number of smokers and an equivalent increase in former smokers. It is also assumed that the initiation rate for new smokers would decrease by 5% to 10%, resulting ultimately in a proportional reduction in the number of smokers, and an equivalent absolute increase in the number of persons who have never smoked. However, the impact of the reduced initiation rate would gradually take place over a 60 year period.

Finally, the estimated value of excess absences per smoker or former smoker is presented in Exhibit 4-2. The average value of each day lost is taken to be approximately $104 per day. This is the weighted average of the median daily earnings of white collar, blue collar, and service workers (weighted by the proportion of the smoking population in each of these categories). The reported earnings are inflated by 24% to account for fringe benefits.[11]

Given that a smoker's average daily earnings including fringe benefits is about $104, and discounting all future effects by 3% yields an estimated savings of under $0.5 billion per year (Exhibit 4-3). This is quite insignificant when compared with other effects. *(See Exhibit S-2 for estimates related to H.R. 3434 under current baseline conditions.)*

Section 5: Savings in Smoking-Related Fires

Smoking is the leading cause of fire deaths in the United States. According to the National Fire Protection Association (NFPA), smoking materials were the cause of more than 200,000 fires per year during the decade of the 1980s (Miller 1993). Smoking-related fires refer to those caused by lighted tobacco products, and not cigarette lighters or matches.

Most smoking-related fire injuries and property losses are in residential environments, which would not be subject to smoking restrictions. For example, between 1988 and 1990, there was an annual average of some 1,328 smoking-related fire fatalities in residences compared to an annual average of 38 fatalities in non-residential buildings (Exhibit 5-1). Likewise, property damage due to smoking-related fires over the same period averaged some $316 million annually for residences, compared to $115 million annually in non-residential buildings.

This study estimates that smoking restrictions comparable to H.R. 3434 would eliminate 90% of the smoking-related fires in the non-residential sector with smoking bans. A 50% reduction in the nonresidential sector with smoking lounges is assumed. Further, because smoking restrictions are postulated to reduce the smoking population through quitting and reduced initiation, a proportional decrease in residential smoking-related fires is also estimated. Estimated reductions in injuries, deaths, and property damage from smoking restrictions in a society having no such restrictions is presented in Exhibit 5-2. Because a large portion of smoking related fatalities is in residences, the annual benefits from smoking restrictions in public buildings is minimal, and would be on the order of $0.6 billion to $0.9 billion per year (Exhibit 5-3). *(See Exhibit S-2 for estimates related to H.R. 3434 under current baseline conditions.)*

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[11] The daily earnings are the BLS median weekly earnings divided by 5. The smoking prevalence rates by labor category are given in DHHS 1989.

Value of Benefits or Losses Regarding Smokers

This analysis assumes that, faced with restrictions on where they may smoke, some current smokers would quit and some would reduce overall consumption. In addition, these restrictions would also tend to discourage many nonsmokers, such as teenagers, from becoming smokers.

These changes in behavior would result in significant improvements to the health of smokers themselves, extension of their life expectancy due to the avoidance of premature death, and reductions in medical expenses during their lifetime, as well as other benefits such as increased safety and reduced property damage from smoking-related fires.

Clearly, these health benefits to smokers are highly significant. However, there remain 46 million smokers who purchase approximately 25 billion packs of cigarettes annually, and about 1 million persons become regular smokers each year. Since smokers do this despite the risks and costs, one would presume that, provided these persons are rational, fully knowledgeable, and are able to accurately assess the consequences of smoking, including potential addiction, the benefits of smoking to them outweigh the risks and costs. However, for a number of reasons, this study does not attempt to estimate the economic value of the benefits or losses regarding smokers.

First, EPA is concerned that the economic measures traditionally applied to the health consequences of pollution may not be appropriate to use in estimating the social value of physical effects of smoking that occur to smokers themselves. Exposure to pollution, such as ETS, is essentially involuntary and uncompensated. Addiction arguments aside, smoking is a voluntary activity that results in other consequences for smokers, some positive and some negative. These other consequences are not reflected in measures of value for health risk reductions sometimes used by EPA. Applying traditional health risk valuation factors to health consequences for smokers would therefore inappropriately omit the value of all these other costs and benefits to smokers, resulting in potentially biased measures of the value change to society.

Second, analysts disagree whether the traditional economic models one might use to measure the welfare change to smokers can be reasonably applied, particularly given limits on available data. To obtain reasonable estimates of the change in net benefits to smokers, these traditional models require that the subjects, smokers in this case, are acting rationally in response to a free and open marketplace. Furthermore, these consumption decisions must either be devoid of significant price distortions such as taxes and subsidies, or analytical corrections must be made to take account of these distortions. With respect to the rationality requirement, questions have been raised whether the rational consumer choice model applies given the apparent addictive nature of smoking.[14] Questions have also been raised whether the consequences of taxes (e.g., cigarette tax) and subsidies (e.g., tobacco farm subsidies, subsidized health care) significantly distort consumer decision making in this case.

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[14] Note, however, that some analysts subscribe to models of "rational addiction" which have been developed and empirically tested (Becker and Murphy,1988); (Chaloupka,1991). However, these models do not take account of those who underestimate the strength of the addiction or who, for whatever reason fail to appreciate the magnitude of the adverse consequences. Nor do they appropriately confront the difficult question of the social consequences from teenage smoking. These models demonstrate that teenagers tend to disregard the future consequences of smoking more so than adults (Chaloupka, 1991).

Third, EPA is concerned that currently available data are insufficient to support using a traditional economic model to estimate the change in net benefit to smokers caused by H.R. 3434. The reason for this is H.R. 3434 does not prohibit smoking outright, nor does it change the purchase price or quantity of cigarettes available. Instead, H.R. 3434 only compels changes in the location and/or time pattern of cigarette consumption. This would be expressed in economic terms as an increase in the transaction cost of smoking, and the transaction cost would vary widely among smokers. Since it is unclear how the slope of the demand curve for cigarettes might shift in response to a nonuniform increase in transaction costs to smokers, a reliable measure of the change in net benefits to smokers cannot be derived.

Based on the foregoing, this study makes no attempt at this time to express the health consequences of H.R. 3434 to smokers themselves in social value terms.

Summary of Costs and Benefits With Reference To A Society With No Smoking Restrictions

This completes the assessment of smoking restrictions using our analytic baseline of a society with no restrictions. The results of this analysis are summarized in Exhibit S-1, and may be interpreted as the costs and benefits of smoking restrictions in a society where no such restrictions exist. This summary analysis forms the basis for estimating the effects that H.R. 3434 would have on current society, which is the subject of the remaining portion of this report.

Effects on Productivity

On-the-Job Productivity Improvements from Reduced ETS. It is generally agreed that ETS reduces the productivity of "individual" building occupants, and that clearly defined and fairly implemented smoking policies will increase "organizational" productivity by reducing potential conflicts between smokers and nonsmokers. While reduced ETS would likely have some positive impact on smoker productivity, the inability to smoke at their work station would likely have the opposite effect.

The ETS effect would *increase* productivity and apply to all employees. However, some smokers would work less effectively and some would spend more time going to and from an allowable smoking area. This may *decrease* productivity, but would apply only to smokers, and only to some proportion of the smoking population. Quantitative estimates of these effects could not be developed for this study.

Benefits from Reduced Absenteeism

After accounting for differences in socioeconomic characteristics between smokers and persons who have never smoked, smokers are estimated to have about 50% more workdays lost than persons who have never smoked, and former smokers are estimated to have about 30% more workdays lost than never smokers (Manning. et al. 1991).

Based on a review of recent studies, it is estimated that between 3% and 6% of current smokers would quit as a result of national legislation that restricts smoking. This would result in an immediate decrease in the number of smokers and an equivalent increase in former smokers. The initiation rate for new smokers is also estimated to decrease by 5% to 10%. This would ultimately result in an equivalent proportional reduction in the number of smokers , and an equivalent absolute increase in the number of persons who have never smoked. The average daily earnings including fringe benefits of smokers is about $104, and discounting all future effects by 3% yields an estimated savings of under $0.5 billion per year.

Savings in Smoking-Related Fires

Most smoking-related fire injuries and property losses are in residential environments, which would not be subject to smoking restrictions. As a result, the savings from smoking restrictions would be minimal, and is estimated to be approximately $0.5 to $0.7 billion per year. This estimate includes the effect of an estimated reduction in cigarette consumption at home because of quitting and reduced initiation.

Social Benefits or Losses Regarding Smokers

Smoking restrictions comparable to those in H.R. 3434 would be expected to result in some reduction in overall cigarette consumption. Faced with restrictions on where they may

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smoke, some current smokers may quit and some may reduce overall consumption. In addition, these restrictions would also tend to discourage many nonsmokers, mostly teenagers),[18] from becoming smokers.

These changes in behavior would result in significant improvements to the health of smokers themselves, as well as other benefits such as increased safety and reduced property damage from smoking-related fires. Based on the assumptions used in this analysis, EPA estimates changes in smoking behavior would result in an average of 27,000 to 54,000 fewer premature deaths per year among smokers during the first 50 years, and 47,000 to 92,000 fewer premature deaths per year thereafter.[19] On average, smokers who quit or cut back would add back an average of 5 to 8 years of life otherwise lost to smoking-related premature death. For those nonsmokers who avoid becoming smokers, life is extended by an average of about 15 years.

Clearly, these health benefits to smokers are highly significant. However, for a number of reasons this study does not attempt to interpret the social value of these changes. First, the economic measures traditionally applied to the health consequences of pollution may not be appropriate to use in estimating the social value of physical effects of smoking which occur to smokers themselves. Exposure to pollution, such as ETS, is essentially involuntary and uncompensated. Addiction arguments aside, smoking is a voluntary activity which results in other consequences for smokers, some positive and some negative. These other consequences are not reflected in measures of value for health risk reductions sometimes used by EPA. Applying such health risk valuation factors to health consequences for smokers would therefore inappropriately omit the value of all these other costs and benefits to smokers, resulting in potentially biased measures of the welfare change to society.

Second, analysts disagree whether the traditional economic models one might use to measure the welfare change to smokers can be reasonably applied, particularly given limits on available data. To obtain reasonable estimates of the change in net benefits to smokers, these traditional models require that the subjects, smokers in this case, are acting rationally in response to a free and open marketplace. Furthermore, these consumption decisions must either be devoid of significant price distortions such as taxes and subsidies, or analytical corrections must be made to take account of these distortions. With respect to the rationality requirement, questions have been raised whether the rational consumer choice model applies given the apparent addictive nature of smoking.[20] Questions have also been raised whether the consequences of taxes (e.g., cigarette tax) and subsidies (e.g., tobacco farm subsidies, subsidized health care) significantly distort consumer decision making in this case.

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[18] CDC (1991).

[19] The difference in death rates each year results from the different time patterns of the effects of quitting and cutting back on consumption, and because the analysis assumed that it would take 60 years reduced annual initiation to complete its effect on the size of the smoking population. Therefore, the 54,000 to 92,000 premature deaths reflect annual rates after 60 years for reduced initiation, In addition, this analysis assumed H.R. 3434 would have only a "one time" effect on decisions to quit, rather than an ongoing effect. Therefore, the H.R. 3434-related quitting eventually disappears as the cohort of smokers motivated to quit by H.R. 3434 dies from old age or other causes.

[20] Note, however, that some analysts subscribe to models of "rational addiction" which have been developed and empirically tested (Becker and Murphy,1988); (Chaloupka,1991). However, these models do not take account of those who underestimate the strength of the addiction or who, for whatever reason fail to appreciate the magnitude of the adverse consequences. Nor do the models appropriately confront the difficult question of the social consequences from teenage smoking. These models demonstrate that teenagers tend to disregard the future consequences of smoking more so than adults (Chaloupka, 1991).

Third, EPA is concerned that currently available data are insufficient to support using a traditional economic model to estimate the change in net benefit to smokers caused by H.R. 3434. The reason for this is that H.R. 3434 does not prohibit smoking outright, nor does it change the purchase price or quantity of cigarettes available. Instead, H.R. 3434 only compels changes in the location and/or time pattern of cigarette consumption. This would be expressed in economic terms as an increase in the transaction cost of smoking, and the transaction cost would vary widely among smokers. Since it is unclear how the slope of the demand curve for cigarettes might shift in response to a nonuniform increase in transaction costs to smokers, a reliable measure of the change in net benefits to smokers cannot be decided.

Based on the foregoing, this study makes no attempt at this time to express the health consequences of H.R. 3434 to smokers themselves in social value terms. Future versions of this analysis may make such an attempt if these analytical problems and data limitations are resolved.

Comparing Costs and Benefits of H.R. 3434

Bearing in mind the limitations presented by the current analysis two principal findings emerge from this analysis. First, it is clear that, for those items quantified in this study, the benefits of smoking restrictions comparable to H.R. 3434 substantially outweigh the costs. Second, comparing the high estimate of costs with the low estimate of benefits does not change the fundamental conclusions that benefits significantly exceed costs.

It should be noted that no attempt was made in the current analysis to evaluate the costs and benefits of altering provisions of the legislation. Throughout this analysis, no exception in scope or timing of the provisions of H.R. 3434 were assumed. Clearly, changing provisions such as the scope or timing of the restrictions would affect both costs and benefits.

Comparisons with Alternative Baselines

Given the rapid increase in public and private smoking restrictions in the last few years, and the downward trend in cigarette consumption, it is likely that the future will bring additional restrictions, and consumption may continue to fall without passage of H.R. 3434. Of course, the future is always uncertain, and tobacco consumption and smoking restrictions will be influenced in part by campaigns of tobacco and anti- smoking interests (Samuels and Glantz, 1991, Macdonald and Glantz, 1994).

Alternative scenarios were also constructed which varied the assumption about future baseline consumption of cigarettes. Similar to other major influences such as the national educational campaigns about smoking, national legislation restricting smoking in public buildings may contribute to continued downward trends in cigarette consumption. Alternatively, these downward trends may continue or level off regardless of the advent of such legislation. However, sensitivity analysis indicates that, as in the case of alternative public and private restriction policies, varying the assumed baseline trend in future cigarette consumption has no significant effect on the result that social benefits would be expected to exceed costs by a substantial margin.

Results using alternative baseline scenarios are summarized in Exhibit S-3. A graphic display is presented in the exhibit. The first scenario presents results under an assumption that there are no restrictions currently in place and that per capita consumption of cigarettes remains at current levels. This is the base scenario used to calculate benefits and costs of smoking restrictions. The second scenario differs from the first in that it assumes that 23% of the population is covered by policies which are comparable to those in H.R. 3434. This is the baseline used to assess the impact of H.R. 3434. The third scenario assumes that restrictive smoking policies will continue to be adopted in the public and private sector without the passage of H.R. 3434, and that these will continue and achieve a level of 75% compliance with standards comparable to requirements of H.R. 3434 in 10 years and remain at that level thereafter. The fourth scenario combines an assumption of 23% existing coverage with an assumption that per capita cigarette consumption will continue to fall for ten years into the future at a 3% per year, and then remain constant after that. The last scenario is the same as the fourth except that per capita cigarette consumption is assumed to fall for 20 years before it levels off.

Under all of the alternative scenarios presented in this analysis, assumptions about the pervasiveness of future restrictions in the absence of H.R. 3434 have virtually no effect on the findings that, for the items quantified in this study, the social benefits would exceed the costs.

A 3% discount rate is used for all scenarios. While the absolute level of estimated costs and benefits are different under each scenario, our qualitative conclusions remain unchanged.

Other Economic Considerations

The estimates of costs and benefits covered in this analysis are a subset of potential economic consequences that policy makers may wish to consider.

Restoration of Lost Income: Implementing smoking restrictive legislation nationally would result in the restoration of approximately $31,000[21] for each pre-retirement year of premature death which is avoided because of smokers who quit, cut back, or fail to become smokers because of H.R. 3434. On average, we estimate that each premature death avoided because of quitting and reduced consumption would add approximately 1.4 to 4 salary earning years, and each premature death avoided from persons who refrain from becoming smokers would add approximately 11 salary earning years of life.[22] When future values are discounted at 3%, this analysis estimates that between $3 billion and $6 billion of lost income would be restored. A similar estimate was not possible for persons exposed to ETS, though this effect should be considered. The importance of this impact is enhanced to the extent that some children, spouses, the elderly or disabled may be dependent on such income.

Reduced Burden on the Medical Service Industry: Every year, the average expenditure for medical services for smokers and former smokers exceeds that of nonsmokers. However, this is partially offset by the fact that nonsmokers live longer, and continue to consume medical services during the extra years of life. When both of these factors are taken into account, the result is a net excess burden on the medical service industry of about $35 billion per year due to smoking.[23] Assuming that changes in the excess medical expenditures due to smoking restrictions would be proportional to changes in smoking-related premature deaths, this analysis estimates that every reduction in annual premature death would represent an annual reduction of $85,000 for medical services. Accordingly, when future savings are discounted at 3%, H.R. 3434 would reduce annual expenditures for medical services by $2.3 billion to $4.7 billion per year. It is not clear from our analysis what net impact reduced exposure to ETS would have on the medical service industry.

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[21] The estimated annual earnings of smokers is inflated by 20% to account for earnings after the age of 65, based on OTA (1993).

[22] Salary earning years are assumed to be years prior to the age of 65.

Potential Cost to Social Security and other Pension Funds: Persons who would otherwise have died prematurely would live longer under smoking restrictions and collect pensions and social security during those extended years. Each premature death avoided for smokers who quit, cut back, or fail to initiate smoking represents an extension of life of about 5 to 7 years beyond the age of 65, during which time they would be eligible to collect a pension annuity. Data are not currently available to support a similar estimate for ETS exposed individuals.

Reduced Revenues from Cigarette Sales and Excise Taxes: Implementation of national legislation to restrict smoking in public buildings would reduce overall cigarette consumption by approximately 11% to 17%, and this impact would occur within the first few years of implementation. This would result in a corresponding reduction in cigarette tax revenues.[24] However, these could be offset, to some extent, by the social benefits of alternative agricultural production or other taxable uses of farmland.

Employment Dislocations: Reductions in demand for cigarettes and medical services would involve some temporary dislocations of persons employed in these industries.

Conclusions

Given data limitations, and the uncertainties inherent in cost-benefit analysis of public health and environmental policies, this analysis does not purport to provide definitive conclusions about the overall merits of national smoking restriction legislation. Nevertheless, while recognizing that several effects of H.R. 3434 including effects on productivity, comfort from reduced exposure to ETS, and the net losses or gains regarding smokers, were not quantified, this analysis demonstrates that, for those items that were quantified, the estimated benefits of H.R. 3434 exceed the estimated costs by a substantial amount. This analysis suggests that the net effect of these excluded items would have to represent a loss exceed $39 billion to $72 billion per year for costs to exceed benefits.

As suggested in Exhibit S-4, the overall findings of substantial net benefits are not altered by comparing high costs to low benefits, or by alternative discount rates. Furthermore, while the magnitude of the net benefits specifically allocated to H. R. 3434 is dependent on one's assumptions about baseline conditions, these assumptions go more to the question of whether or not to capture these net benefits through national legislation or by other public and/or private initiatives.

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[23] This is estimated from information provided by Hodgson (1992) who compares excess medical costs over the lifetime of persons who have ever smoked, and persons who have never smoked. Similar data and procedures were also used by Manning. et al. (1991).

[24] For an excellent comparison of what smokers pay in excise taxes, medical expenditures, and contribution to retirement funds, relative to the value of the services they receive for those payments, see Manning. et al. (1991). However, the net monetary payments made by or to smokers is not a useful index for measuring the overall social benefits or costs of smoking restrictions. As previously described, willingness to pay measures are more appropriate. Also, our costs and benefits do not count transfers of costs or benefits from one group in society to others.

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